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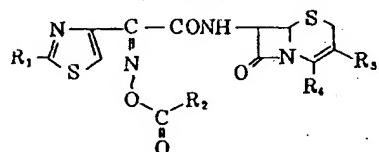
### Specification

#### 1. Title of the Invention:

Novel Cephem Compounds

#### 2. Scope of the Patent Claims

(1) A cephem compound, or pharmaceutically permissible salt thereof, indicated by the following general formula:



(within the formula, R<sub>1</sub> indicates an amino group or a protected amino group; R<sub>2</sub> indicates a C<sub>1</sub> to C<sub>4</sub> lower alkyl group; R<sub>3</sub> indicates a vinyl group, lower alkylthio group, -CH=CHCOOR'<sub>3</sub> (wherein R'<sub>3</sub> indicates a hydrogen atom or a lower alkyl group), or -CH<sub>2</sub>COOR''<sub>3</sub> (wherein R''<sub>3</sub> indicates a hydrogen atom or a lower alkyl group); and R<sub>4</sub> indicates a carboxyl group or a protected carboxyl group).

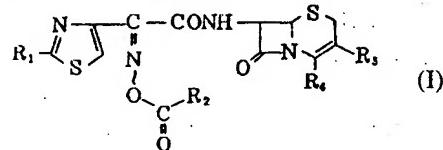
(2) The syn isomer of the compound according to claim 1.

#### 3. Detailed Description of the Invention

The present invention relates to novel cephem compounds and pharmaceutically permissible salts thereof.

Presently numerous cephalosporin type compounds are being sold commercially. Although such compounds are being used clinically, only few such compounds can be administered orally (i.e., cephalexin, cefatrizine, [misspelling of "cefactor"], cefroxadine, etc.). Thus the inventors of the present invention, with the intent of searching for a cephalosporin compound capable of oral administration that is effective against drug-resistant bacteria and that has a wide antibacterial spectrum, examined substitution of various types of substituent groups at the 7 position and the 3 position of the cephalosporin nucleus. The present invention was attained during this investigation by the discovery that specific cephem compounds had a wide antibacterial spectrum and had excellent infection treatment effect when administered orally.

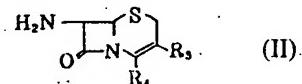
That is to say, the present invention is a novel cephem compound having the excellent antibacterial activity of the present invention. In particular, the present invention provides a cephem compound, or pharmaceutically permissible salt thereof, having the following general formula: (I)



(within the formula, R<sub>1</sub> indicates an amino group or a protected amino group; R<sub>2</sub> indicates a C<sub>1</sub> to C<sub>4</sub> lower alkyl group; R<sub>3</sub> indicates a vinyl group, lower alkylthio group, -CH=CHCOOR'<sub>3</sub> (wherein R'<sub>3</sub> indicates a hydrogen atom or a lower alkyl group), or -CH<sub>2</sub>COOR''<sub>3</sub> (wherein R''<sub>3</sub> indicates a hydrogen atom or a lower alkyl group); and R<sub>4</sub> indicates a carboxyl group or a protected carboxyl group).

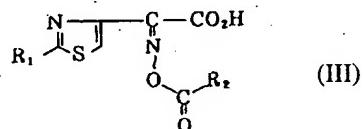
Compound (I) of the present invention may be synthesized, for example, by several methods such as the example methods listed below.

#### ① General Formula (II)



(within the formula, R<sub>3</sub> and R<sub>4</sub> have the same meanings as indicated previously.)

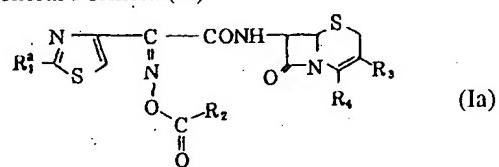
The compound indicated by this general formula and/or N-silyl adduct indicated by General Formula (III) are manufactured.



(within the formula, R<sub>1</sub> and R<sub>2</sub> have the same meanings as indicated previously.)

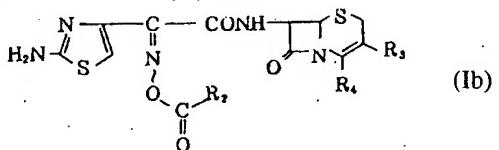
Alternatively, an adduct having reactivity at the carboxyl group of the compound indicated by the later formula is reacted, and then the protective group is removed to manufacture the compound of the present invention shown in formula (I).

#### ② General Formula (Ia)



(within the formula, R<sub>1</sub><sup>a</sup> indicates a protected amino group; and R<sub>2</sub>, R<sub>3</sub>, and R<sub>4</sub> have the same meanings as indicated previously.)

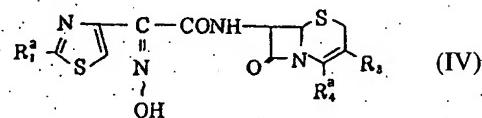
After the protective groups of the compound indicated by this formula are removed, the compound of General Formula (Ib) is manufactured.



(within the formula, R<sub>2</sub>, R<sub>3</sub>, and R<sub>4</sub> have the same meanings

as indicated previously.)

#### ③ General Formula (IV)



(within the formula, R<sub>4</sub><sup>a</sup> indicates a protected carboxyl group; and R<sub>1</sub><sup>a</sup> and R<sub>3</sub> have the same meanings as indicated previously.)

The compound indicated by the above formula is reacted with a compound of the general formulae (V) or (VI).

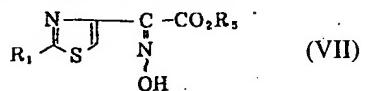


(within the formula, X indicates a halogen atom; and R<sub>2</sub> has the same meaning as indicated previously.)

After this reaction, if required, the protective group is removed to manufacture the present compound shown in formula (I).

For the above mentioned formulae (I) through (VI), the term "lower" is taken to mean a carbon number of 1 through 4, unless stated otherwise. Any normal protective group, as may be required, capable of deprotection may be used as the amino protective group indicated by R<sub>1</sub><sup>a</sup>. Examples that can be used with advantage are the 2,2,2-trichloroethoxycarbonyl group, methylsulfonylethoxy carbonyl group, t-butoxycarbonyl group, chloroacetyl group, trityl group, and the like. The carboxyl protective group indicated by R<sub>4</sub><sup>a</sup> is any such group normally used with β-lactam type compounds. Examples that can be cited are the diphenylmethyl group, p-nitrobenzyl group, trichloroethyl group, p-methoxybenzyl group, allyl group, and the like. Moreover, examples that can be cited of the adduct having the reactive carboxyl group of compound (III) are acid halide compounds, acid azides, acid anhydrides, mixed acid anhydrides, active amides, active esters, and the like. Moreover, examples that can be cited of the halogen atom of compound (V) and compound (VI) are chlorine, bromine, and iodine.

The formula (III) compound, which is the raw material of the method ① of the present invention, can be manufactured, for example, by reaction of the compound of General Formula (VII).



(within the formula, R<sub>5</sub> indicates a carboxyl protective group; and R<sub>1</sub> has the same meaning as indicated previously.)

The above mentioned compound is reacted with a compound of the following formula (V) or (VI).



(within the formula,  $R_2$  and X have the same meanings as indicated previously.)

After this reaction, if required, the protective group is removed to manufacture the compound.

The reaction between the compound (VII) and the compound (V) or (VI) is carried out in the presence of a base and in an organic solvent, water, or a water-containing solvent. Removal of the carboxyl protective group must be carried out under conditions that do not cause cleavage-decomposition of the acyl group of the oxime, do not cause decomposition of the oxymimino [sic] group, and the like. Thus a method is adopted such as the method of using an acyl group as the  $R_5$  group and reductive removal using palladium catalyst (Journal of Organic Chemistry, 47-587, 1982). Alternatively, a method can be adopted of using a t-butyl group, p-methoxybenzyl group, or diphenylmethyl group as  $R_5$  and deprotection by hydrolysis in acid.

During the method ① of the present invention, when the adduct having the reactive carboxyl group of the formula (III) compound is used, the reaction is preferably carried out below the freezing point of water in a solvent that does not adversely affect the reaction (e.g., acetone, dioxane, acetonitrile, chloroform, methylene chloride, tetrahydrofuran, ethyl acetate, and the like). Moreover, when the formula (III) compound is used in the free form, this reaction is preferably carried out in the presence of a condensation agent. Examples that can be cited of the condensation agent include so-called Vilsmeier reagents, which are obtained by the reaction of  $N,N'$ -dicyclohexylcarbodiimide,  $N$ -cyclohexyl- $N'$ -morpholinoethylcarbodiimide,  $N$ -cyclohexyl- $N'$ -(4-diethylaminocyclohexyl)carbodiimide,  $N,N'$ -diethylcarbodiimide,  $N,N'$ -diisopropylcarbodiimide,  $N$ -ethyl- $N'$ -(3-dimethylaminopropyl)carbodiimide,  $N,N'$ -carbonyl-bis(2-methylimidazole), pentamethyleneketen- $N$ -cyclohexylimine, diphenylketen- $N$ -cyclohexylimine, ethoxyacetylene, 1-alkoxy-1-chloroethylene, trialkyl phosphite, ethyl polyphosphate, isopropyl polyphosphate, phosphorus oxychloride, phosphorus trichloride, thionyl chloride, oxalyl chloride, triphenylphosphine, a 2-ethyl-7-hydroxy benzisoxazolium salt, a 2-ethyl-5-

(m-sulfophenyl) isoxazolium hydroxide intramolecular salt, 1-(p-chlorobenzene sulfonyloxy)-6-chloro-1H-benzotriazole, or dimethylformamide with thionyl chloride, phosgene, phosphorus oxychloride, or the like.

This reaction may be carried out in the presence of an inorganic or organic base. Examples that can be cited of the base includes alkali metal hydrogen carbonates such as sodium hydrogen carbonate, potassium hydrogen carbonate, and the like; alkaline earth metal carbonates such as calcium carbonate and the like; tri-(lower) alkylamines such as triethylamine, trimethylamine, and the like; pyridine;  $N$ -(lower) alkylmorpholines;  $N,N'$ -di-(lower) alkylbenzylamines, and the like.

Reaction temperature is not limited, and the reaction is normally carried out under cooling or heating.

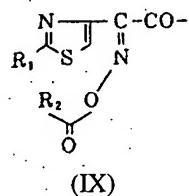
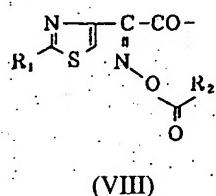
For the present invention, the syn isomer of the desired compound (I) can be obtained as the syn isomer produced by the reaction between the compound (II) and the compound (III), for example, by reacting under neutral conditions in the presence of the above mentioned Vilsmeier reagent.

Moreover, the reaction of the present invention method ③ can itself be carried out by known methods. That is to say, the reaction with the compound (IV) or (V), is carried out in a solvent (e.g. methylene chloride, ethyl acetate, tetrahydrofuran, and the like) in the presence of an organic base (e.g., pyridine, triethylamine, and the like) or an inorganic base (e.g., potassium carbonate, sodium hydrogen carbonate, and the like) at a temperature of -20°C to 20°C. Moreover, the reaction between the compound (IV) and the compound (VI) is preferably carried out at a temperature of 0°C to 5°C in a solvent such as dimethylformamide, dimethylsulfoxide, and the like.

Furthermore, for each of the methods ① through ③ of the present invention, removal of the protective group can be carried out by a known method according to the type of protective group. The protective group can be removed, for example, by adopting a method such as hydrolysis using an acid, hydrolysis using a base, the reduction method, and the like.

Although syn and anti isomers exist for the present invention compound (I), and the compounds (Ia), (Ib), and the raw material compounds (III), (IV), and (VII), the present invention includes both isomers as well as any mixture of such isomers.

Here the syn and anti isomers of the desired compound (I) are taken to mean the geometric isomers having the following respective partial structures (VIII) and (IX).



(within the formulae, R<sub>1</sub> and R<sub>2</sub> have the same meanings as mentioned previously.)

When the compound of the present invention has a free carboxyl group and / or free amino group, it is possible to form a pharmaceutically permissible salt by the normal methods. This salt is a normal non-toxic salt, and examples of such salts are alkali metal salts such as a sodium salt, a potassium salt, and the like; alkaline earth metal salts such as a calcium salt, a magnesium salt, and the like; an ammonium salt; salts with organic bases such as organic amine salts (e.g., a trimethylamine salt, a triethylamine salt, a pyridine salt, a picoline salt, a dicyclohexylamine salt, a N,N'-dibenzylethylenediamine salt, and the like); organic acid salts such as those of acetic acid, maleic acid, tartaric acid, methane sulfonic acid, benzenesulfonic acid, formic acid, toluenesulfonic acid, and the like; salts of inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, and the like; and salts with amino acids such as arginine, asparaginic acid, glutaminic acid, and the like; and the like.

The subject compound (I) of the present invention and the pharmaceutically permissible salts thereof are novel compounds that display strong anti-microbial activity. This compound inhibits the growth of a wide range of pathogenic microorganisms including both Gram positive and Gram negative microorganisms. This compound is particularly useful as an antibiotic that is administered orally. During administration of the compound (I) that is the subject of the present invention and the pharmaceutically permissible salts thereof with the

object of medical treatment, the compound can be administered in the form of a normal formulation intermixed with a pharmaceutically permissible carrier. Examples that can be cited of the carrier, are an agent in the solid or liquid inherent form, which is inorganic or organic, and which is suitable for oral administration, non-oral administration, or topical administration. Moreover, examples that can be cited of the form of the formulation include a capsule, tablet, sugar-coated tablet, soft capsule, suppository, solution, suspension, emulsion, and the like.

In order to show the usefulness of the subject compound provided by the present invention, results of an examination of the antibiotic effect of representative compounds, among the compounds of the present invention, will be indicated below.

### 1. Antibiotic activity

#### (a) Test method

Testing was carried out by the agar plate dilution method. The minimum growth inhibiting concentration (MIC) at which growth of the various test microorganism did not occur was observed and is recorded in Table 1. These results are shown in Table 1.

#### (b) Test compounds

- A: trifluoroacetic acid salt of 7-[2-(2-aminothiazol-4-yl)-2-acetoxyiminoacetoamido]-3-methylthio-3-cephem-4-carboxylic acid (syn isomer)
- B: trifluoroacetic acid salt of 7-[2-(2-aminothiazol-4-yl)-2-pivaloyloxyiminoacetoamido]-3-methylthio-3-cephem-4-carboxylic acid (syn isomer)
- C: trifluoroacetic acid salt of 7-[2-(2-aminothiazol-4-yl)-2-propionyloxyiminoacetoamido]-3-methylthio-3-cephem-4-carboxylic acid (syn isomer)
- D: trifluoroacetic acid salt of 7-[2-(2-aminothiazol-4-yl)-2-isobutyloxyiminoacetoamido]-3-methylthio-3-cephem-4-carboxylic acid (syn isomer)
- E: trifluoroacetic acid salt of 7-[2-(2-aminothiazol-4-yl)-2-pivaloyloxyiminoacetoamido]-3-ethylthio-3-cephem-4-carboxylic acid (syn isomer)
- F: sodium salt of 7-[2-(2-aminothiazol-4-yl)-2-pivaloyl

oxyiminoactoamido]-3-methoxycarbonylmethyl-3-cephem-4-carboxylic acid

G: trifluoroacetic acid salt of 7-[2-(2-aminothiazol-4-yl)-2-pivaloyloxyiminoactoamido]-3-vinyl-3-cephem-4-carboxylic acid (syn isomer)

(space left intentionally blank hereinafter)

Test microorganism	Test compound						
	A	B	C	D	E	F	G
Sta. aureus 606	0.78	1.56	0.78	0.78	25	6.25	1.56
Sta. aureus 606 E 25	0.78	1.56	0.78	0.78	25	3.13	1.56
Sta. aureus 209P JC-1	0.20	0.39	0.20	0.39	6.25	1.56	0.39
Sta. aureus Smith (1)	0.20	0.78	0.20	0.39	12.5	1.56	0.78
Sta. epidermidis ATCC 14990	0.20	0.78	0.20	0.37	6.25	1.56	0.78
B. subtilis ATCC 6633	0.39	0.78	0.39	0.39	12.5	3.13	0.78
E. coli W3630 RGN823	0.78	6.25	0.78	1.56	12.5	12.5	6.25
E. coli W3630 RGN14	0.78	12.5	1.56	3.13	12.5	25	6.25
E. coli W3630 RGN238	1.56	6.25	1.56	1.56	12.5	25	6.25
E. coli ML1410	0.78	12.5	1.56	3.13	12.5	25	12.5
E. coli [sic] NIHJ JC-2	0.78	3.13	0.78	1.56	12.5	12.5	6.25
E. coli No.29	0.39	3.13	0.78	0.78	12.5	6.25	3.13
Kleb. pneumoniae GN69	0.39	1.56	0.39	0.78	6.25	6.25	1.56
Kleb. pneumoniae GN118	0.39	3.13	0.39	0.78	6.25	12.5	3.13
Kleb. pneumoniae PCI602	0.78	3.13	0.39	0.78	6.25	12.5	3.13
Pro. mirabilis GN79	1.56	6.25	25	3.13	25	25	3.13
Pro. mirabilis GN310						12.5	25
Sal. typhi O-901-W	0.39	0.78	0.20	0.39	6.25	6.25	0.78

Test microorganism	Test compound						
	A	B	C	D	E	F	G
Sal. typhimurium LT-2	0.39	3.13	0.39	0.78	12.5	12.5	1.56
Sal. enteritidis No.11	0.20	0.20	0.10	0.10	6.25	0.78	0.20
Shigella dysenteriae Shigae	0.20	0.78	0.20	0.39	6.25	3.13	0.78
Pro. vulgaris GN76	1.56	6.25	6.25	12.5	50	12.5	3.13
Pro. vulgaris GN106	0.78	3.13	1.56	3.13	50	12.5	3.13
Pro. vulgaris OX-19						12.5	12.5
Pro. morganii Kono						25	50
Pro. rettgeri GN624	0.20	1.56	0.39	0.78	6.25	3.13	3.13
Pro. rettgeri J-0026	0.20	0.78	0.20	0.39	6.25	1.56	1.56
E. coli GN206						6.25	6.25
Citro. freundii GN346/16	1.51	6.25	0.78	1.56	12.5	25	6.25
Enter. cloacae G-0005						50	12.5
Enter. cloacae G-0008			6.25	6.25	25	25	6.25
Serr. marcescens No. 1	1.51	6.25	3.13	3.13	25	25	6.25
Serr. marcescens No. 2	3.13		3.13	3.13	25	50	12.5
Ps. cepacia M-0527	1.56	12.5	3.13	3.13	12.5	12.5	12.5
Str. faecalis W-75					12.5		

## 2. Infection and medical treatment experiment

### (a) Test method

The test animal for this test was the ICR-JCL strain of mouse (4 week old,  $20 \pm 0.5$  g body weight) used in groups of 3 animals per 1 group. The microorganism culture used for infection was Escherichia Coli (Escherichra [sic] Coli) no. 29. This was pre-cultured for 20 hr. at  $37^{\circ}\text{C}$  in heart infusion agar, and thereafter the microorganism was suspended in isotonic sodium chloride aqueous solution. After mixing in MUEIN to give a concentration of 2.5%, this was injected into the abdominal cavity of the mouse. Various concentrations of the drug sample were administered orally immediately after microbial infection, and the number of surviving mice was observed after 7 days. These results are shown in Table 2.

### (b) Test compound

H: pivaloyloxymethyl ester of 7-[2-(2-aminothiazol-4-yl)-2-acetoxyiminoacetoamido]-3-methylthio-3-cephem-4-carboxylic acid (syn isomer)

I: pivaloyloxymethyl ester of 7-[2-(2-aminothiazol-4-yl)-2-pivaloyloxyiminoacetoamido]-3-methylthio-3-cephem-4-carboxylic acid (syn isomer)

Table 2

Administered quantity (mg/mouse)	Survival rate						
	A*	B*	E*	H	I	Cefroxadine	Non-treated control group
10	3/3	3/3	3/3	3/3	3/3	3/3	0/3
1	3/3	3/3	3/3	3/3	3/3	2/3	0/3
0.1	0/3	2/3	2/3	2/3	2/3	0/3	0/3

\* The test compounds A, B, and E are the same as those listed earlier.

Although reference examples and working examples are used as follows to explain the present invention in detail, the present invention is not limited by these working examples.

### Reference example 1

ethyl-2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetate (syn

isomer):

A solution of aceto ethyl acetate (30 g) in 30 mL of glacial acetic acid was stirred and ice cooled. A solution of sodium nitrite (18 g) in 40 mL of water was added to this solution at a sufficiently slow rate to maintain reaction temperature at less than or equal to 10°C. After about 30 min. of mixing while ice cooling, a solution of 16 g of potassium chloride in 80 mL of water was then added. The generated mixture was then mixed for 1 hr. The lower organic layer was removed, and the aqueous layer was extracted using diethyl ether. The extract was combined with the oily material, and this was washed in turn using a saturated sodium chloride aqueous solution, followed by drying and then concentration-solidification to obtain 30 g of ethyl-2-hydroxyimino-3-oxobutylate (syn. isomer). A solution of 1.5 g of ethyl-2-hydroxyimino-3-oxobutylate (syn isomer) in 40 mL of methylene chloride was stirred and ice cooled. Then 14 g of sulfonyl chloride was added dropwise, and the mixture was stirred for 2 days. After a water wash, the mixture was dried and concentrated. Then 17 g of the oily residue was dissolved in 50 mL of ethanol. Then 7.7 mL of dimethylaniline and 4.2 g of thiourea were added while stirring. After 2 hr, the product was recovered by filtration. This was washed with ethanol to obtain 7 g of the indicated compound.

m. p. 188°C (decomposition)

#### Reference example 2

ethyl-2-(2-tritylaminothiazol-4-yl)-2-hydroxyiminoacetate  
(syn isomer):

A solution of 13 g of the product of reference example 1 in dimethylformamide (30 mL) containing 8.4 mL of triethylamine was stirred and cooled (-30°C). Then 16.75 g of trityl chloride was added over 2 hr. After the mixture was stirred at this temperature for 30 min., the mixture was stirred for 17 hr at room temperature.

The reaction product was washed with (distributed between) 500 mL of water and 500 mL of ethyl acetate. The organic layer was separated out and was washed with water, followed by stirring with 500 mL of 1N HCl. The precipitate was collected and then was washed in turn using water, ethyl acetate, and ether, followed by drying to obtain 16.4 g of the indicated compound as a white solid.

m. p. 184°C to 186°C (decomposition)

#### Reference example 3

sodium 2-(2-tritylaminothiazol-4-yl)-2-hydroxyiminoacetate  
(syn isomer):

First 20 g of ethyl 2-(2-tritylaminothiazol-4-yl)-2-hydroxyiminoacetate hydrochloride (syn isomer) was suspended in 400 mL of ethanol. While cooling on ice, 400 mL of 1N NaOH aqueous solution was added dropwise. After 24 hr of stirring at room temperature, the precipitate that formed was recovered by filtration. After ether washing of the precipitate, the precipitate was then suspended in 500 mL of tetrahydrofuran. While cooling on ice, the mixture was adjusted to pH = 2.0 using 10% HCl to obtain a uniform solution. Thereafter under ice cooling, pH was adjusted to 8.0 using saturated aqueous sodium bicarbonate solution, and a precipitate formed. After recovery by filtration, the precipitate was washed in turn using water and ether. The precipitate was dried to obtain 16 g of white powder.

#### Reference example 4

allyl 2-(2-tritylaminothiazol-4-yl)-2-hydroxyiminoacetate  
(syn isomer):

First 1.8 g of sodium 2-(2-tritylaminothiazol-4-yl)-2-hydroxyiminoacetate (syn isomer) was dissolved in 20 mL of dimethylformamide. Under ice cooling, 0.8 mL of allyl iodide was added to this solution, and the mixture was stirred for 24 hr at room temperature. Then a mixed solution of 200 mL ethyl acetate / 200 mL water was added to this mixture, and the organic layer was water washed (200 mL × 2). After drying over magnesium sulfate, the mixture was concentrated and solidified. The obtained material was purified by Wako GEL C-200, 60 g (system = toluene - ethyl acetate). The yield was 1.3 g.

NMR (80 MHz, δ value, ppm, CDCl<sub>3</sub>):

4.85 (2H, m), 5.25 - 5.50 (2H, m), 5.95 (1H, m), 6.90 (1H, s), 7.85 (16H, b. s)

#### Reference example 5

allyl 2-(2-tritylaminothiazol-4-yl)-2-acetoxyiminoacetate  
(syn isomer):

First 469 mg of allyl 2-(2-tritylaminothiazol-4-yl)-2-hydroxyiminoacetate (syn isomer) was dissolved in 10 mL of dry methylene chloride. Under ice cooling, 0.1 mL of pyridine was added. Thereafter 1 mL of dry methylene chloride containing 0.1 mL of acetyl chloride was added dropwise, and the mixture was stirred at the same temperature for 20 min. The

mixture was water washed, and then dried over magnesium sulfate. After concentration and solidification, the mixture was purified using silica gel [chromatography] to obtain 500 mg of the subject compound.

FD mass = 511

IR (Nujol) = 3300, 1740 cm<sup>-1</sup>

NMR (80 MHz, δ value, ppm):

2.11 (3H, s), 4.75 - 4.85 (2H, m), 5.20 - 5.48 (2H, m), 5.70 - 6.15 (1H, m), 6.85 (1H, s), 7.80 (15H, s)

In the same manner as reference example 5, allyl 2-(2-tritylaminothiazol-4-yl)-2-hydroxyiminoacetate (syn isomer) was reacted with the corresponding acid chlorides to obtain the following compounds of reference examples 6 - 8.

#### Reference example 6

allyl 2-(2-tritylaminothiazol-4-yl)-2-propionyloxyiminoacetate (syn isomer):

FD mass = 525

IR (Nujol) = 3300, 1740 cm<sup>-1</sup>

NMR (80 MHz, δ value, ppm):

1.25 (3H, t, J = 8 Hz), 2.5 (2H, q, J = 8 Hz), 4.75 - 4.85 (2H, m), 5.20 - 5.48 (2H, m), 5.70 - 6.15 (1H, m), 6.82 (1H, s), 7.80 (15H, s)

#### Reference example 7

allyl 2-(2-tritylaminothiazol-4-yl)-2-isobutyroxyiminoacetate (syn isomer):

FD mass = 540

IR (Nujol) = 3300, 1745 cm<sup>-1</sup>

NMR (80 MHz, δ value, ppm):

1.25 (6H, d, J = 8 Hz), 2.60 (1H, m), 4.70 - 4.82 (2H, m), 5.15-5.48 (2H, m), 5.70 - 6.15 (1H, m), 6.85 (1H, s), 7.20 (16H, s)

#### Reference example 8

allyl 2-(2-tritylaminothiazol-4-yl)-2-pivaloyloxyiminoacetate (syn isomer):

FD mass = 553

IR (Nujol) = 3300, 1740 cm<sup>-1</sup>

NMR (80 MHz, δ value, ppm):

1.25 (9H, s), 4.70 - 4.85 (2H, m), 5.16 - 5.55 (2H, m), 5.65 - 6.20 (1H, m), 6.90 (1H, s), 7.26 (16H, s)

#### Reference example 9

2-(2-tritylaminothiazol-4-yl)-2-acetyloxyiminoacetic acid (syn isomer):

First 250 mg of allyl 2-(2-tritylaminothiazol-4-yl)-2-acetyloxyiminoacetate (syn isomer) was dissolved in 10 mL of dry methylene chloride. Under ice cooling, 5 mL of an ethyl acetate solution containing 85 mg of potassium 2-ethylhexanoate was added, followed by addition of 12 mg of triphenylphosphine and 12 mg of palladium (0) tetrakis phosphine. This mixture was stirred at the same temperature for 1 hr. Thereafter the resultant precipitate was recovered by filtration and then was washed in turn using isopropyl ether and ethyl acetate. The precipitate was then dried to obtain potassium 2-(2-tritylaminothiazol-4-yl)-2-acetyloxyiminoacetate. The obtained potassium salt was then suspended in 20 mL of ethyl acetate, and then pH was adjusted to 2.0 using 5% HCl solution under ice cooling. The mixture was washed using a saturated sodium chloride aqueous solution and then dried. After concentration and solidification, 130 mg of the subject compound was obtained as a white powder.

NMR (80 MHz, δ value):

2.15 (3H, s), 6.80 (1H, s), 7.30 (16H, b. s)

In the same manner as reference example 9, an allyl 2-(2-tritylaminothiazol-4-yl)-2-alkylacyloxyiminoacetate (syn isomer) was used as raw material, and potassium 2-ethylhexanoate was used in the presence of palladium catalyst to obtain the following compounds of reference examples 10 - 12.

#### Reference example 10

2-(2-tritylaminothiazol-4-yl)-2-propionyloxyiminoacetic acid:

NMR (80 MHz, δ value, ppm, CDCl<sub>3</sub>):

1.25 (3H, t, J = 8 Hz), 2.5 (2H, q, J = 8 Hz), 6.80 (1H, s), 7.30 (16H, b. s)

**Reference example 11**

2-(2-tritylaminothiazol-4-yl)-2-isobutyloxyiminoacetic acid:  
 NMR (80 MHz,  $\delta$  value, ppm,  $\text{CDCl}_3$ ):  
 1.05 (6H, d,  $J = 8$  Hz), 2.40 (1H, m), 6.85 (1H, s), 7.30 (16H, b. s)

**Reference example 12**

2-(2-tritylaminothiazol-4-yl)-2-pivaloyloxyiminoacetic acid:  
 NMR (80 MHz,  $\delta$  value, ppm,  $\text{CDCl}_3$ ):  
 1.16 (9H, s), 6.80 (1H, s), 7.28 (16H, b. s)

**Reference example 13**

p-nitrobenzyl 7- $\beta$ -phenylacetamido-3-methylthio-3-cephem-4-carboxylate:

After 5.6 g (12 mM) of p-nitrobenzyl 7- $\beta$ -phenylacetamido-3-hydroxy-3-cephem-4-carboxylate was suspended in 4.0 mL of dry acetonitrile, the suspension was cooled to -20°C under a nitrogen atmosphere while stirring, and then 2.4 mL of diisopropyl-ethylamine and 2.8 mL of diphenylchlorophosphate were added. The reaction mixture was stirred for about 30 min. at this temperature to obtain a transparent solution. Completion of the reaction was confirmed by TLC. Thereafter the reaction mixture was cooled to -30°C, and then 2.4 mL of diisopropyl-ethylamine was added. About 3 g of methyl mercaptan was injected in the reaction mixture below the agitator. The reaction was continued for about 2 hr while stirring at -25°C to -30°C (precipitation out of crystals). After completion of the reaction was confirmed using TLC, 0.5 mL of acetic acid was added.

The reaction product was collected and then was washed in turn using 7 mL of cold acetonitrile and 10 mL of isopropyl ether. Thereafter the reaction product was dried. Recovered quantity = 4.95 g (yield = 83%).

m. p. = 231°C (decomposition)

IR (Nujol) = 3230, 1775 ( $\beta$ -lactam); 1705, 1650  $\text{cm}^{-1}$

UV  $\lambda_{\max}$  = 319 nm

NMR ( $\text{DMSO-d}_6 + \text{CDCl}_3$ ):  $\delta$  value (60 MHz)

3.28 (3H, s), 3.61 (2H, s), 3.68 (2H, s), 5.03 (1H, d, ( $J = 4.6$  Hz)), 5.73 (2H, s), 5.64 (1H, d, d, ( $J = 4.6$  Hz,  $J = 7.8$  Hz)), 7.29 (5H, s), 7.63, 8.20 (4H, 2xd, ( $J = 8.2$ )), 8.83 (1H, d, ( $J = 7.8$ )).

**Reference example 14**

7-phenylacetamido-3-methylthio-3-cephem-4-carboxylic acid:

2.5 g of p-nitrobenzyl 7-phenylacetamido-3-methylthio-3-cephem-4-carboxylate (m. p. = 231°C (decomposes)) was added to 15 mL of dioxane and 10 mL of 85% formic acid. The mixture was heated to 50°C to 55°C, and then 1.5 - 3 g of zinc powder was added as several alloquates while stirring. The mixture was allowed to react for 2 - 5 hr. After confirmation of completion of the reaction using thin layer chromatography (TLC), the mixture was cooled to room temperature, and non-dissolved material was collected. This was washed using dioxane. The reaction solution and the wash solution were combined, and then most of the solvent was removed under vacuum. Then while a mixture of 10 mL of ethyl acetate and 50 mL of ice water was stirred, pH was adjusted to 7.0 - 7.5 using sodium hydrogen carbonate, and then the reaction solution was added gradually dropwise. After addition of the entire reaction solution, non-dissolved material was collected and water washed. The water layer and the wash solution were combined and were extracted several times using ethyl acetate. The organic layer was washed with a small quantity of water, and the aqueous layers were combined. If necessary, this is treated with activated carbon. The water layer was adjusted to a pH of 1 - 2 and was placed overnight in a freezer. The resultant solids were collected. After water washing, the solids were washed with a small quantity of isopropyl ether and then were dried to obtain the subject compound. Recovered quantity = 1.4 g (77%). After recrystallization from acetone + isopropyl ether:

m. p. = 197°C to 198°C (decomposition)

UV  $\lambda_{\max}$  = 318 nm (95% ethanol)

IR (Nujol) = 3280 (NH), 1770 ( $\beta$ -lactam), 1690, 1640  $\text{cm}^{-1}$

NMR ( $\text{DMSO-d}_6 + \text{CDCl}_3$ ):  $\delta$  value (60 MHz (R600))

2.33 (3H, s), 3.57 (2H, s), 3.67 (2H, s), 5.01 (1H, d,  $J = 4.7$  Hz), 5.56 (1H, d, d,  $J = 4.7, 8.2$  Hz), 7.25 (5H, s), 9.01 (1H, d,  $J = 8.2$  Hz)

**Reference example 15**

diphenylmethyl 7-phenylacetamido-3-methylthio-3-cephem-4-carboxylate:

1.82 g of the 7-phenylacetamido-3-methylthio-3-cephem-4-

carboxylic acid obtained during reference example 14 was dissolved in heated acetone. Then a solution of diazodiphenylmethane in n-hexane was added under agitation. After the reaction was carried out overnight while monitoring the reaction with TLC, the reaction mixture was concentrated under vacuum and was dried-solidified. The solids were treated with an excess of diazodiphenylmethane, which was then removed. The solids were then dissolved in methylene chloride, and pH was adjusted to 7.5 using a sodium hydrogen carbonate aqueous solution. The methylene chloride layer was recovered and was dried, followed by drying-solidification under vacuum. The solids were treated with isopropyl ether and ethyl ether, followed by drying to obtain the subject compound. Recovered quantity = 2.4 g (90%). After recrystallization from acetone + methanol:

m. p. = 162°C to 163°C (decomposition)

UV  $\lambda_{\text{max}}$  = 318 nm (95% ethanol)

IR (Nujol) = 3230 (NH), 1780 ( $\beta$ -lactam), 1700 (ester), 1650  $\text{cm}^{-1}$

NMR ( $\text{CDCl}_3$ ):  $\delta$  value (60 MHz)

1.99 (3H, s), 2.91, 3.38 (2H, ABq,  $J$  = 1.68 Hz), 3.64 (2H, s), 4.95 (1H, d,  $J$  = 4.3 Hz), 5.62 (1H, d, d,  $J$  = 4.3, 8.6 Hz), 6.86 (1H, s), 7.2 - 7.33 (16H)

#### Reference example 16

diphenylmethyl 7-amino-3-methylthio-3-cephem-4-carboxylate, hydrogen chloride salt:

2.65 g of the diphenylmethyl 7-phenylacetamido-3-methylthio-3-cephem-4-carboxylate obtained during reference example 15 was dissolved in 50 mL of methylene chloride, and the solution was cooled to -30°C. Then 4 mL of water-free pyridine was added to this solution, and then 3.2 g of fine powder phosphorous pentachloride was added. The mixture was heated gradually, and the mixture was stirred for about 3 hr at -10°C to 10°C. After confirmation of the completion of the reaction using TLC, the reaction mixture was cooled to -40°C. (A portion of the reaction mixture was sampled and was treated separately by addition of anhydrous methanol. The chromatographic solvent was benzene / ethyl acetate = 2 / 1.) Then 15 mL of anhydrous methanol was added dropwise to this reaction solution (crystal precipitation). The transparent reaction solution was heated gradually and was stirred for about 1 hr at -10°C. After confirmation of completion of the reaction using TLC, 40 mL of cooled sodium chloride aqueous solution was

added, and the mixture was reacted for about 1 hr under ice cooling while stirring and maintaining the pH at 1.5 - 2.0 using dilute ammonia water. The precipitate was collected and was washed in turn using a small quantity of ice water, ethyl acetate, and isopropyl ether. The precipitate was then dried to obtain the subject compound. Recovered quantity = 2.25 g (91%).

m. p. = 203°C to 205°C (decomposition)

UV  $\lambda_{\text{max}}$  = 319 nm (95% ethanol)

IR (Nujol) = 1780 ( $\beta$ -lactam), 1760, 1700  $\text{cm}^{-1}$

NMR ( $\text{DMSO-d}_6$ ):  $\delta$  value (60 MHz)

2.44 (3H, s), 3.73, 4.13 (2H, ABq,  $J$  = 16 Hz), 5.08 (1H, d,  $J$  = 4.3 Hz), 5.28 (1H, d,  $J$  = 4.3 Hz), 6.90 (1H, s), 7.20 - 7.80 (13H, m)

#### Reference example 17

benzydryl 7-amino-3-ethylthio-3-cephem-4-carboxylate, hydrogen chloride salt:

The subject compound was obtained based upon reference examples 13 - 16.

m. p. = 172°C to 173°C (decomposition)

UV  $\lambda_{\text{max}}$  = 319 nm (95% ethanol)

IR (Nujol) = 1778, 1705  $\text{cm}^{-1}$

NMR ( $\text{DMSO-d}_6$ ):  $\delta$  value (60 MHz)

1.16 (3H, t,  $J$  = 7 Hz), 2.93 (2H, q,  $J$  = 7 Hz), 2.93 (2H, q,  $J$  = 7 Hz), 3.68, 4.10 (2H, ABq,  $J$  = 15 Hz), 5.05 (1H, d,  $J$  = 5 Hz), 5.77 (1H, d,  $J$  = 5 Hz), 6.83 (1H, s), 7.3 (10H, m)

#### Reference example 18

diphenylmethyl 7-phenylacetamido-3-vinyl-3-cephem-4-carboxylate:

After 1.2 g of diphenylmethyl 7-phenylacetamido-3-bromoethyl-3-cephem-4-carboxylate was dissolved in 2 mL of dimethylformamide, 818 mg of triphenyl phosphine and 311 mg of sodium iodide were added. The mixture was stirred for 17 hr at 0°C to 5°C. The reaction solution was washed with isopropyl ether and was powdered. Then this was washed further using ethyl acetate. The obtained powder was suspended in 30 mL of methylene chloride. Then 15 mL of a 36% formaldehyde solution was added to this mixture under ice cooling. Thereafter pH was adjusted to 9.0 using a saturated sodium hydrogen carbonate aqueous solution. The mixture was stirred for 30 min. under ice cooling and then was stirred for 2 hr at room temperature. Then pH was adjusted to 5.0 using 5% HCl under ice cooling, and then the mixture was extracted using methylene

chloride. After a water wash, [the organic layer] was dried over magnesium sulfate. The mixture was concentrated and solidified, followed by purification by chromatography (40 g, Wako GEL C-200, toluene - ethyl acetate system) to obtain 420 mg of the subject compound.

IR (Nujol) = 1765, 1710 cm<sup>-1</sup>

NMR (80 MHz, δ value, ppm, CDCl<sub>3</sub>):

3.30, 3.60 (2H, ABq, J = 19 Hz), 3.56 (2H, s), 4.91 (1H, d, J = 4.8 Hz), 5.16 (1H, d, J = 8 Hz), 5.36 (1H, d, J = 15 Hz), 5.75 (1H, d, d, J = 4.8, 9.0 Hz), 6.25 (1H, d, J = 9.0 Hz), 6.89 (1H, s), 7.10 - 7.55 (16H, m)

#### Reference example 19

diphenylmethyl 7-amino-3-vinyl-3-cephem-4-carboxylate, hydrogen chloride salt:

After 230 mg of diphenylmethyl 7-phenylacetamido-3-vinyl-3-cephem-4-carboxylate was dissolved in 10 mL of dry methylene chloride, the solution was cooled to -40°C. Then 0.36 mL of pyridine and 282 mg of phosphorous pentachloride were added, and the mixture was stirred for at -40°C for 2 hr and at 0°C for 2hr. Thereafter the reaction mixture was cooled to -50°C, and 1 mL of dry methanol was added. The mixture was stirred for 2 hr at -50°C and then 1 hr at 0°C. Then 10 mL of saturated sodium chloride aqueous solution was added to the reaction mixture under ice cooling, and the reaction mixture was stirred for 30 min. at 0°C to 5°C. Then 20 mL of isopropyl ether was added, and the resultant precipitate was collected by filtration. The precipitate was washed in turn using isopropyl ether and ethyl acetate to obtain 164 mg of the subject compound.

IR (Nujol) = 1760, 1705 cm<sup>-1</sup>

NMR (60 MHz, δ value, ppm, DMSO-d<sub>6</sub>):

3.73, 4.00 (2H, ABq, J = 18 Hz), 5.1 - 5.4 (2H, m), 5.58 (1H, d, J = 6 Hz), 5.93 (1H, m), 6.97 (1H, s), 7.00 (1H, d, d, J = 12, 18 Hz), 7.42 (10H, m), 9.17 (2H, m)

#### Reference example 20

ethoxycarbonyloxyethyl 7-amino-3-methylthio-3-cephem-4-carboxylate, hydrogen chloride salt (α form):

After 481 mg of ethoxycarbonyloxyethyl 7-phenylacetamido-3-methylthio-3-cephem-4-carboxylate (α form) (m. p. = 157°C to 158°C) (0.001 mol) was dissolved in 20 mL of

methylene chloride, 0.40 mL of pyridine was added, and the mixture was cooled to -20°C. Then 440 mg of phosphorous pentachloride was added; under agitation the mixture was gradually heated to +5°C to +10°C; and the mixture was reacted for about 90 min. (30 min. after disappearance of the phosphorous pentachloride). The reaction solution was cooled to -30°C, and then 5.0 mL of a methylene chloride solution of 2.0 mL isobutanol was added dropwise. Thereafter, the mixture was heated gradually to +5°C to +10°C, and the mixture was reacted for 2 hr (reaction tracked by TLC). After completion of the reaction, the reaction mixture was cooled to 0°C, and then 5 mL of cooled water containing 2 mL of aqueous sodium chloride [solution] was poured in while stirring. The mixture was stirred for about 60 min. under ice cooling. Then 10 mL of diisopropyl ether and 10 mL of ethyl ether were added. Precipitation of white crystals immediately increased. The crystals were washed using diisopropyl ether and ether. Recovered quantity = 360 mg.

m. p. = 148°C to 150°C (decomposition)

UV λ<sub>max</sub> = 321 nm (95% ethanol)

IR (Nujol) = 1781, 1762, 1700 cm<sup>-1</sup>

#### Reference example 21

ethoxycarbonyloxyethyl 7-phenylacetamido-3-ethylthio-3-cephem-4-carboxylate, hydrogen chloride salt:

990 mg (0.002 mol) of ethoxycarbonyloxyethyl 7-amino-3-ethylthio-3-cephem-4-carboxylate (m. p. = 130°C to 131°C) was used for reaction and treatment in the same manner as reference example 20 to obtain 750 mg (90.8%) of the subject compound.

m. p. = 188°C to 190°C (decomposition)

UV λ<sub>max</sub> = 320 nm (95% ethanol)

IR (Nujol) = 1780, 1763, 1710 cm<sup>-1</sup>

#### Reference example 22

p-nitrobenzyl 7-phenylacetamido-3-methoxycarbonylmethyl-3-cephem-4-carboxylate:

After 4.7 g of p-nitrobenzyl 7-phenylacetamido-3-hydroxy-3-cephem-4-carboxylate was dissolved in 35 mL of dimethylformamide, 4 g of carbomethoxy methylene triphenyl phosphorane was added, and the mixture was stirred for 24 hr at room temperature. The reaction mixture was concentrated and was dissolved in 500 mL of ethyl acetate. This was washed in turn using cold 5% HCl, water, and saturated sodium chloride

aqueous solution. The solution was then dried over magnesium sulfate. The mixture was concentrated and solidified next under vacuum, and the obtained residue was purified by column chromatography (Wako GEL C-200, 200 g, toluene - ethyl acetate system) to obtain 28 g of the subject compound.

IR (Nujol) = 3300, 1760 cm<sup>-1</sup>

NMR (80 MHz, δ value, ppm, CDCl<sub>3</sub>):

3.20 - 3.75 (9H, m), 5.00 (1H, d, J = 4.8 Hz), 5.30 (2H, b. s), 5.85 (1H, d, d, J = 4.8 Hz, 9 Hz), 6.15 (1H, d, J = 9 Hz), 7.35 (5H, s), 7.55, 8.22 (4H, ABq, J = 9 Hz)

During the above mentioned reaction, 882 mg of a byproduct (isomer of the double bond of the cephalosporin nucleus) was obtained. This byproduct was oxidized by peroxide by the normal method and then was reduced using phosphorous trichloride to obtain a substance that was identical to the subject compound.

### Reference example 23

diphenylmethyl 7-phenylacetamido-3-methoxycarbonylmethyl-3-cephem-4-carboxylate:

First 2.8 g of p-nitrobenzyl 7-phenylacetamido-3-methoxycarbonylmethyl-3-cephem-4-carboxylate was dissolved in 50 mL of formic acid and 50 mL of ethanol under ice cooling. Then 1.8 g of zinc powder was added over 10 min. while stirring. After stirring for 1 hr at room temperature and 2 hr at 50°C, insolubles were recovered by filtration. The filtrate solution was concentrated under vacuum, and then a mixed solution of 50 mL of ethyl acetate and 20 mL of water was added. While cooling on ice, pH was maintained at 7.0 by addition of saturated sodium hydrogen carbonate aqueous solution. The insolubles were removed, and the aqueous layer was washed using ethyl acetate. After adjustment of pH of the aqueous layer to 2.0 using 5% HCl under ice cooling, the aqueous layer was extracted using ethyl acetate.

Then a diphenyldiazomethane - n-hexane solution was added to the organic layer, and the mixture was reacted at room temperature. After the raw material (carboxylic acid) had disappeared, the mixture was concentrated and solidified under vacuum. The residue was washed with isopropyl ether to obtain 1.27 g of the subject compound.

IR (Nujol) = 3320, 1770 cm<sup>-1</sup>

NMR (80 MHz, δ value, ppm, CDCl<sub>3</sub>):

3.32 - 3.70 (9H, m), 4.95 (1H, d, J = 4.8 Hz), 5.80 (1H, d.d, J = 4.8 Hz, 9.6 Hz), 6.10 (1H, d, J = 9.6 Hz), 6.85 (1H, s), 7.15 - 7.35 (16H, m)

### Reference example 24

diphenylmethyl 7-amino-3-methoxycarbonylmethyl-3-cephem-4-carboxylate:

After 1.12 g of phosphorous pentachloride was dissolved in 20 mL of methylene chloride, 1.45 mL of pyridine was added under ice cooling. The mixture was stirred for 30 min. at this same temperature and then was cooled to -50°C. Thereafter 10 mL of methylene chloride solution containing 1.0 g of diphenylmethyl 7-phenylacetamido-3-methoxycarbonylmethyl-4-carbonate was added, and the reaction mixture was stirred at -50°C for 2 hr and then was stirred under ice cooling for 2 hr. The mixture was cooled to -50°C, and then 4 mL of dry methanol was added dropwise. The mixture was stirred for 1 hr at 0°C, and 20 mL of saturated sodium chloride aqueous solution was added under ice cooling. The mixture was stirred at the same temperature for 30 min. After extraction using methylene chloride, the mixture was washed using saturated sodium chloride aqueous solution. Thereafter pH was adjusted to 7.0 using sodium hydrogen carbonate aqueous solution under ice cooling. After drying, the mixture was concentrated and solidified; followed by purification by Wako GEL-C200 (15 g, toluene - ethyl acetate system) to obtain 350 mg of the subject compound.

IR (Nujol) = 1780 cm<sup>-1</sup>

NMR (80 MHz, δ value, CDCl<sub>3</sub>):

1.70 (2H, b. s), 3.36 - 3.65 (7H, m), 4.70 (1H, d, J = 4.8 Hz), 4.96 (1H, d, J = 4.8 Hz), 6.90 (1H, s), 7.20 - 7.40 (10H, m)

### Reference example 25

diphenylmethyl 7-phenylacetamido-3-methoxycarbonylmethyl-3-cephem-4-carboxylate:

After 1.2 g of diphenylmethyl 7-phenylacetamido-3-bromomethyl-3-cephem-4-carboxylate was dissolved in 2 mL of dimethylformamide, 818 mg of diphenyl phosphine and 311 mg of sodium iodide were added. The reaction mixture was stirred at 5°C for 20 hr. The mixture was concentrated under vacuum, and was powdered using isopropyl ether. This was washed further using ethyl acetate.

The obtained salt was dissolved in 30 mL of methylene chloride, and 580 mg of methyl glyoxalate mono-hydrate was added to this solution. The mixture was ice cooled, and pH was adjusted to 9 using saturated sodium hydrogen carbonate

aqueous solution. The mixture was stirred for 4 hr at room temperature. Thereafter under ice cooling, pH was adjusted to 5.0 using 5% hydrochloric acid aqueous solution, and the resultant solution was extracted with methylene chloride. After water washing, the solution was dried over magnesium sulfate, followed by concentration and solidification. The residue was purified by Wako GEL C-200 (20 g, toluene - ethyl acetate system) to obtain 184 mg of the subject compound.

IR (Nujol) = 1780 cm<sup>-1</sup>

NMR (80 MHz, δ value, ppm, CDCl<sub>3</sub>):

3.40 - 3.65 (7H, m), 5.0 (1H, d, J = 4.2 Hz), 6.70 (1H, d, J = 12 Hz), 6.8 (1H, d, d, J = 4.2 Hz, 9.6 Hz), 6.15 (1H, d, J = 9.6 Hz), 6.80 (1H, s), 6.82 (1H, d, J = 12 Hz), 7.20 - 7.40 (16H, m)

#### Reference example 2

diphenylmethyl 7-amino-3-methoxycarbonylvinyl-3-cephem-4-carboxylate:

After 164 mg of phosphorous pentachloride was dissolved in 2 mL of methylene chloride under a nitrogen gas purge, the solution was ice cooled, and 0.21 mL of pyridine was added. The mixture was stirred for 30 min. at the same temperature. Separately, 1.5 mL of methylene chloride containing 150 mg of diphenylmethyl 7-phenylacetoamido-3-methoxycarbonylvinyl-3-cephem-4-carboxylate was prepared and was added dropwise to the previous solution at -50°C over about 10 min. After stirring of the reaction mixture for 30 min. at -50°C and then 2 hr at 0°C to 5°C, the reaction mixture was cooled to -50°C. Then 2 mL of methanol cooled to -50°C was added dropwise to the reaction solution. Thereafter the reaction mixture was stirred for 30 min. at -50°C and 1 hr at 0°C to 5°C. Then 3 mL of saturated sodium chloride aqueous solution was added, and the mixture was stirred at the same temperature for 30 min. The mixture was extracted with methylene chloride and then was washed using a saturated sodium chloride aqueous solution. In the presence of the saturated sodium chloride aqueous solution, pH was adjusted to 7.0 using a 2% sodium hydrogen carbonate aqueous solution, and [the organic layer] was water washed. The mixture was dried over magnesium sulfate and was concentrated - solidified. After purification by Wako GEL C-200 (2g, toluene - ethyl acetate system), 73 mg of the subject compound was obtained.

IR (Nujol) = 1780 cm<sup>-1</sup>

NMR (80 MHz, δ value, ppm, CDCl<sub>3</sub>):

1.75 (2H, b. s), 3.40 (2H, b. s), 3.56 (3H, s), 4.7 (1H, d, J = 4.2 Hz), 4.9 (1H, d; J = 4.8 Hz), 5.75 (1H, d, J = 12 Hz), 6.85 (1H, d, J = 12 Hz), 6.90 (1H, s), 7.2 - 7.4 (10H, m)

#### Working example 1

diphenylmethyl 7-[2-tritylaminothiazol-4-yl]-2-pivaloyloxyiminoacetoamide]-3-vinyl-3-cephem-4-carboxylate (syn isomer):

After 192 mg of diphenylmethyl 2-(2-tritylaminothiazol-4-yl)-2-pivaloyloxyiminoacetic acid (syn isomer), 120 mg of diphenylmethyl 7-amino-3-vinyl-3-cephem-4-carbonate, and 50 mg of 1-hydroxybenzotriazole were dissolved in 10 mL of methylene chloride, the solution was cooled over ice. Then 1 mL of methylene chloride containing 75 mg of dicyclohexylcarbodiimide was added, and the mixture was stirred at 5°C overnight. The mixture was concentrated under vacuum, and the residue was dissolved in 50 mL of ethyl acetate. The insolubles were removed; the mixture was cooled; and the mixture was washed in turn using cold 5% hydrochloric acid aqueous solution and saturated sodium chloride aqueous solution. After drying over magnesium sulfate, the mixture was concentrated and solidified under vacuum. The residue was purified by Wako GEL C-200 (8 g, toluene - ethyl acetate system) to obtain 200 mg of the subject compound.

IR (Nujol) = 1770, 1740 - 1710 cm<sup>-1</sup>

NMR (80 MHz, δ value, ppm, CDCl<sub>3</sub>):

1.30 (9H, s), 3.50 (2H, b. s), 5.05 (1H, d, J = 5 Hz), 5.20 (1H, d, J = 8 Hz), 5.40 (1H, d, J = 14.5 Hz), 5.90 (1H, d, d, J = 5 Hz, J = 9.5 Hz), 6.90 (2H, b. s), 6.65 - 7.10 (1H, m), 7.15 - 7.40 (26H, m)

#### Working example 2

diphenylmethyl 7-[2-(2-tritylaminothiazol-4-yl)-2-acetyl oxyiminoacetoamido]-3-vinyl-3-cephem-4-carboxylate (syn isomer):

Diphenylmethyl 2-(2-tritylaminothiazol-4-yl)-2-acetyloxyiminoacetic acid was used as raw material in the same manner as during working example 1 to obtain the subject compound.

IR (Nujol) = 3300, 1770 cm<sup>-1</sup>

NMR (80 MHz, δ value, ppm, CDCl<sub>3</sub>):

2.70 (3H, s), 5.0 (1H, d, J = 4.8 Hz), 5.2 (1H, d, J = 10

Hz), 5.4 (1H, d, J = 16 Hz), 5.8 (1H, d, d, J = 4.8 Hz, J = 9.0 Hz), 6.8 (1H, s), 6.9 (1H, s), 7.1 - 7.3 (27H, m)

### Working example 3

7-[2-(2-aminothiazol-4-yl)-2-pivaloyloxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylate, trifluoroacetic acid salt (syn isomer):

After 200 mg of diphenylmethyl 7-[2-(2-tritylaminothiazol-4-yl)-2-pivaloyloxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylate (syn isomer) was dissolved in 0.4 mL of anisole, 4 mL of trifluoroacetic acid was added under ice cooling, and the mixture was stirred at the same temperature for 1 hr. The mixture was concentrated under vacuum, and was powdered using isopropyl ether, followed by washing and drying to obtain 85 mg of the subject compound.

IR (Nujol) = 1760 cm<sup>-1</sup>

NMR (80 MHz, δ value, ppm, DMSO-d<sub>6</sub>):

1.15 (9H, s), 3.50, 3.86 (2H, ABq, J = 17.6 Hz), 5.16 (1H, d, J = 5 Hz), 5.35 (1H, d, J = 9 Hz), 5.60 - 5.78 (2H, m), 6.75 - 7.10 (1H, m), 6.95 (1H, s)

### Working example 4

diphenylmethyl 7-[2-(2-tritylaminothiazol-4-yl)-2-pivaloyloxyiminoacetamido]-3-methoxycarbonylmethyl-3-cephem-4-carboxylate (syn isomer):

After 256 mg of 2-(2-tritylaminothiazol-4-yl)-2-pivaloyloxyiminoacetic acid, 181 mg of diphenylmethyl 7-amino-3-methoxycarbonylmethyl-3-cephem-4-carbonate, and 67 mg of 1-hydroxybenzotriazole were dissolved in 20 mL of methylene chloride, the solution was cooled over ice. Then 1 mL of methylene chloride containing 103 mg of dicyclohexylcarbodiimide was added, and the mixture was stirred at 5°C overnight. The mixture was concentrated under vacuum. The residue was dissolved in 30 mL of ethyl acetate, and the insolubles were removed. The mixture was washed in turn using cold 5% hydrochloric acid aqueous solution and saturated sodium chloride aqueous solution. After drying over magnesium sulfate, the mixture was concentrated and solidified under vacuum. The residue was purified by Wako GEL C-200 (15 g, toluene - ethyl acetate system) to obtain 100 mg of the subject

compound.

IR (Nujol) = 3300, 1780 cm<sup>-1</sup>

NMR (80 MHz, δ value, ppm, CDCl<sub>3</sub>):

1.16 (9H, s), 3.40 - 3.70 (7H, m), 5.10 (1H, d, J = 5 Hz), 5.8 (1H, d, d, J = 5 Hz, J = 9.6 Hz), 6.8 (1H, s), 6.85 (1H, s), 7.2 - 7.4 (26H, m)

### Working example 5

sodium 7-[2-(2-aminothiazol-4-yl)-2-pivaloyloxyiminoacetamido]-3-methoxycarbonylmethyl-3-cephem-4-carboxylate:

After 200 mg of diphenylmethyl 7-[2-(2-tritylaminothiazol-4-yl)-2-pivaloyloxyiminoacetamido]-3-methoxycarbonylmethyl-3-cephem-4-carboxylate was dissolved in 0.2 mL of anisole, 2 mL of trifluoroacetic acid was added under ice cooling, and the mixture was stirred at the same temperature for 30 min. Thereafter the mixture was concentrated under vacuum, and was powdered using isopropyl ether. The obtained powder was dried, and then the powder was dissolved in 2 mL water - 2 mL acetic acid. Then a 2% sodium hydrogen carbonate aqueous solution was used to adjust pH to 7.0 under ice cooling. After the aqueous layer was washed with ethyl acetate, the mixture was purified by chromatography (15 mL, DIAION HP-20). The target fraction was concentrated and freeze-dried to obtain 63 mg of the subject compound.

IR (Nujol) = 1770 cm<sup>-1</sup>

NMR (80 MHz, δ value, D<sub>2</sub>O):

1.15 (9H, s), 3.40 - 3.7 (7H, m), 5.0 (1H, d, J = 4.8 Hz), 5.8 (1H, d, J = 4.8 Hz), 6.8 (1H, s)

### Working example 6

7-[2-(2-aminothiazol-4-yl)-2-pivaloyloxyiminoacetamido]-3-(2-methoxycaronylvinyl-3-cephem-4-carboxylic acid, trifluoroacetic acid salt (syn isomer):

IR (Nujol) = 1770 cm<sup>-1</sup>

NMR (80 MHz, δ value, ppm, DMSO-d<sub>6</sub>):

1.20 (9H, s), 3.4 (2H, d), 3.6 (3H, s), 5.0 (1H, d, J = 4.2 Hz), 5.7 (1H, d, J = 12 Hz), 5.80 (1H, d, d, J = 4.2 Hz, 9.6 Hz), 6.7 (1H, s), 6.8 (1H, d, J = 12 Hz)

**Working example 7**

diphenylmethyl 7-[2-(2-aminothiazol-4-yl)-2-acetyloxyiminoacetamido]-3-methylthio-3-cephem-4-carboxylate (syn isomer):

After 120 mg of 2-(2-tritylaminothiazol-4-yl)-2-acetyloxyiminoacetic acid (syn isomer) and 101 mg of diphenylmethyl 7-amino-3-methylthio-3-cephem-4-carbonate were dissolved in 10 mL of dry methylene chloride, 33 mg of 1-hydroxybenzotriazole was added. Under ice cooling, 1 mL of methylene chloride containing 50 mg of dicyclohexylcarbodiimide was added, and the mixture was stirred at 5°C overnight. The insolubles were removed by filtration, followed by washing in turn using 2.5% hydrochloric acid aqueous solution and water. The mixture was then washed, concentrated, and solidified. The residue was then purified by silica gel chromatography. (Wako GEL C-200, 8 g; toluene - ethyl acetate system) to obtain 160 mg of the subject compound.

IR (Nujol) = 1770, 1740 - 1710 cm<sup>-1</sup>

NMR (80 MHz, δ value, ppm, CDCl<sub>3</sub>):

2.20 (3H, s), 2.26 (3H, s), 3.54 (2H, b. s), 5.05 (1H, d, J = 5.0 Hz), 5.75 (1H, d, d, J = 5.0 Hz, 9.0 Hz), 7.86 (1H, s), 7.90 (1H, s), 7.00 - 7.45 (27H, m)

In the same manner as during working example 7, a 2-(2-tritylaminothiazol-4-yl)-2-alkyloxyiminoacetic acid and the corresponding 7-amino-3-cephem adduct were used to obtain the compounds of working examples 8 - 11.

**Working example 8**

diphenylmethyl 7-[2-(2-tritylaminothiazol-4-yl)-2-propionoxyiminoacetamido]-3-methylthio-3-cephem-4-carboxylate (syn isomer):

IR (Nujol) = 1770, 1740 - 1710 cm<sup>-1</sup>

NMR (80 MHz, δ value, ppm, CDCl<sub>3</sub>):

1.25 (3H, t, J = 8 Hz), 2.26 (3H, s), 2.48 (2H, q, J = 8 Hz), 3.55 (2H, b. s), 5.06 (1H, d = 5 Hz) [sic], 5.75 (1H, d, d, J = 5 Hz, 9 Hz), 6.85 (1H, s), 6.92 (1H, s), 7.10 - 7.42 (27H, m)

**Working example 9**

diphenylmethyl 7-[2-(2-tritylaminothiazol-4-yl)-2-isobutyloxyiminoacetamido]-3-methylthio-3-cephem-4-carboxylate (syn isomer):

NMR (80 MHz, δ value, ppm, CDCl<sub>3</sub>):

1.20 (6H, d, J = 8 Hz), 2.24 (3H, s), 2.70 (1H, m), 3.50 (2H, b. s), 5.06 (1H, d, J = 5 Hz), 5.75 (1H, d, d, J = 5 Hz, 10 Hz), 6.86 (1H, s), 6.90 (1H, s); 7.05 - 7.35 (27H, m)

**Working example 10**

diphenylmethyl 7-[2-(2-tritylaminothiazol-4-yl)-2-pivaloyloxyiminoacetamido]-3-methylthio-3-cephem-4-carboxylate (syn isomer):

NMR (80 MHz, δ value, ppm, CDCl<sub>3</sub>):

1.27 (9H, s), 2.26 (3H, s), 3.35, 3.65 (2H, ABq, J=16 Hz), 5.03 (1H, d, J = 5 Hz), 5.78 (1H, d, d, J = 5 Hz, 9 Hz), 6.90 (1H, s), 6.95 (1H, s), 7.15 - 7.40 (27H, m)

**Working example 11**

diphenylmethyl 7-[2-(2-tritylaminothiazol-4-yl)-2-pivaloyloxyiminoacetamido]-3-ethylthio-3-cephem-4-carboxylate (syn isomer):

IR (Nujol) = 3300, 1780, 1740 - 1720 cm<sup>-1</sup>

NMR (80 MHz, δ value, ppm, CDCl<sub>3</sub>):

1.20 (3H, t, J = 8H), 1.25 (9H, s), 2.70 (2H, q, J = 8 Hz), 3.45 (2H, b. s), 5.05 (1H, d, J = 4.8 Hz), 5.70 (1H, d, d, J = 4.8 Hz, 9 Hz), 6.85 (1H, s), 6.90 (1H, s), 7.15 - 7.32 (26H, b. s)

**Working example 12**

7-[2-(2-aminothiazol-4-yl)-2-acetooxyiminoacetamido]-3-methylthio-3-cephem-4-carboxylate, trifluoroacetic acid salt (syn isomer):

First 150 mg of diphenylmethyl 7-[2-(2-tritylaminothiazol-4-yl)-2-acetooxyiminoacetamido]-3-methylthio-3-cephem-4-carboxylate was added to 0.2 mL of anisole under ice cooling and was dissolved. Then 2 mL of trifluoroacetic acid was added at the same temperature, and the mixture was stirred under ice cooling for 1 hr.

Thereafter the trifluoroacetic acid was concentrated under vacuum, and isopropyl ether was added to the residue, which was powdered. The obtained powder was washed sufficiently with isopropyl ether and then ether. Thereafter the mixture was separated using centrifugal separation. The obtained [mixture] was dried under vacuum to obtain 5.5 mg of the subject compound.

IR (Nujol) = 1770 cm<sup>-1</sup>

NMR (80 MHz, δ value, ppm, DMSO-d<sub>6</sub>):

2.16 (3H, s), 2.32 (3H, s), 3.75 (2H, s), 5.12 (1H, d, J = 4.8 Hz), 5.68 (1H, d, d, J = 4.8 Hz, J = 7.5 Hz), 7.10 (1H, s), 9.78 (1H, d, J = 7.5 Hz)

In the same manner as during working example 12, the protective group of the corresponding protected 3-cephalosporin compound was removed by trifluoroacetic acid, and the following compounds of working examples 13 - 16 were obtained.

**Working example 13**

7-[2-(2-aminothiazol-4-yl)-2-propionyloxyiminoacetamido]-3-methylthio-3-cephem-4-carboxylate, trifluoroacetic acid salt (syn isomer):

IR (Nujol) = 1760 cm<sup>-1</sup>

NMR (80 MHz, δ value, ppm, DMSO-d<sub>6</sub>):

1.25 (3H, t, J = 8 Hz), 2.26 (3H, s), 2.50 (2H, q, J = 8 Hz), 5.05 (1H, d, J = 5.0 Hz), 5.70 (1H, d, d, J = 5.0 Hz, J = 8 Hz), 7.05 (1H, s), 9.80 (1H, d, J = 8 Hz)

**Working example 14**

7-[2-(2-aminothiazol-4-yl)-2-isobutyloxyiminoacetamido]-3-methylthio-3-cephem-4-carboxylate, trifluoroacetic acid salt (syn isomer):

IR (Nujol) = 1760 cm<sup>-1</sup>

NMR (80 MHz, δ value, ppm, DMSO-d<sub>6</sub>):

1.15 (6H, d, J = 7.5 Hz), 2.3 (3H, s), 2.65 (1H, m), 3.70 (2H, b, s), 5.15 (1H, d, J = 5 Hz), 5.70 (1H, d, d, J = 5 Hz, J = 8.2 Hz), 7.05 (1H, s), 9.85 (1H, d, J = 8.2 Hz)

**Working example 15**

7-[2-(2-aminothiazol-4-yl)-2-pivaloyloxyiminoacetamido]-3-methylthio-3-cephem-4-carboxylate, trifluoroacetic acid salt (syn isomer):

IR (Nujol) = 3300, 1770 cm<sup>-1</sup>

NMR (80 MHz, δ value, ppm, DMSO-d<sub>6</sub>):

1.2 (9H, s), 2.30 (3H, s), 3.75 (2H, b, s), 5.15 (1H, d, J = 5 Hz), 5.70 (1H, d, d, J = 5 Hz, J = 9 Hz), 7.05 (1H, s), 9.85 (1H, d, J = 9 Hz)

**Working example 16**

7-[2-(2-aminothiazol-4-yl)-2-pivaloyloxyiminoacetamido]-3-ethylthio-3-cephem-4-carboxylate, trifluoroacetic acid salt (syn isomer):

IR (Nujol) = 1760 cm<sup>-1</sup>

NMR (80 MHz, δ value, ppm, DMSO-d<sub>6</sub>):

1.20 (3H, t, J = 8 Hz), 1.25 (9H, s), 2.70 (2H, q, J = 8 Hz), 3.70 (2H, b, s), 5.15 (1H, d, J = 5 Hz), 5.72 (1H, d, d, J = 5 Hz, J = 8 Hz), 7.1 (1H, s), 9.80 (1H, d, J = 8 Hz)

**Working example 17**

pivaloyloxymethyl 7-[2-(2-tritylaminothiazol-4-yl)-2-acetooxyiminoacetamido]-3-methylthio-3-cephem-4-carboxylate (syn isomer):

After 120 mg of 2-(2-tritylaminothiazol-4-yl)-2-acetooxyiminoacetic [poorly legible] acid (syn isomer) and 90 mg of pivaloyloxymethyl 7-amino-3-methylthio-3-cephem-4-carbonate were dissolved in 10 mL of dry methylene chloride,

33 mg of 1-hydroxybenzotriazole was added. Thereafter under ice cooling, 1 mL of methylene chloride containing 50 mg of dicyclohexylcarbodiimide was added, and the mixture was stirred at 5°C overnight. The insolubles were removed by filtration, followed by washing in turn using 2.5% hydrochloric acid aqueous solution and water. After drying, the solution was concentrated under vacuum to dry and solidify the residue. The resultant residue was then purified by silica gel chromatography to obtain 130 mg of the subject compound.

IR (Nujol) = 3300, 1770, 1740 - 1710 cm<sup>-1</sup>

NMR (80 MHz, δ value, ppm, CDCl<sub>3</sub>):

1.20 (9H, s), 2.15 (3H, s), 2.3 (3H, s), 3.55 (2H, b. s), 5.05 (1H, d, J = 4.8 Hz), 5.15 - 5.35 (3H, m), 6.85 (1H, s), 6.95 (1H, d, J = 8 Hz), 7.15 - 7.35 (16H, m)

#### Working example 18

pivaloyloxymethyl 7-[2-(2-tritylaminothiazol-4-yl)-2-pivaloyloxyiminoacetamido]-3-methylthio-3-cephem-4-carboxylate:

In the same manner as that during working example 17, the subject compound was obtained from the corresponding 3-cephem compound.

NMR (80 MHz, δ value, ppm, CDCl<sub>3</sub>):

1.25 (9H, s), 1.30 (9H, s), 2.35 (3H, s), 3.55 (2H, b. d), 5.10 (1H, d, J = 5 Hz), 5.60 - 5.95 (3H, m), 6.85 (1H, d, J = 8 Hz), 6.95 (1H, s), 7.20 - 7.35 (16H, m)

#### Working example 19

pivaloyloxymethyl 7-[2-(2-aminothiazol-4-yl)-2-acetyloxyiminoacetamido]-3-methylthio-3-cephem-4-carboxylate (syn isomer):

After 100 mg of pivaloyloxymethyl 7-[2-(2-tritylaminothiazol-4-yl)-2-acetyloxyiminoacetamido]-3-methylthio-3-cephem-4-carboxylate (syn isomer) was dissolved in 0.1 mL of anisole, the solution was ice cooled. Then 1 mL of trifluoroacetic acid was added, and the mixture was stirred at the same temperature for 1 hr. Thereafter isopropyl ether was added

for powder formation. The obtained powder was washed sufficiently in turn using isopropyl ether and ether. The powder was dissolved in 10 mL of ethyl acetate, and pH was adjusted to 7.0 using 5% sodium hydrogen carbonate aqueous solution under ice cooling. After the organic layer was water washed, the organic layer was dried over magnesium sulfate. The solution was then concentrated and solidified to obtain 3.8 mg of the subject compound.

IR (Nujol) = 1760 cm<sup>-1</sup>

NMR (80 MHz, δ value, CDCl<sub>3</sub>):

1.25 (9H, s), 2.20 (3H, s), 2.35 (3H, s), 3.60 (2H, b. s), 5.10 (1H, d, J = 5 Hz), 5.70 - 5.95 (3H, m), 6.90 (1H, s), 8.25 (1H, d, J = 8 Hz)

#### Working example 20

pivaloyloxymethyl 7-[2-(2-aminothiazol-4-yl)-2-pivaloyloxyiminoacetamido]-3-methylthio-3-cephem-4-carboxylate (syn isomer):

The subject compound was obtained in the same manner as working example 19.

NMR (80 MHz, δ value, CDCl<sub>3</sub>):

1.25 (9H, s), 1.30 (9H, s), 2.35 (3H, s), 3.65 (2H, b. s), 5.10 (1H, d, J = 5 Hz), 5.70 - 5.95 (3H, m), 6.95 (1H, s), 7.60 (1H, d, J = 8 Hz)

The end.

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Amendment of Proceedings (self originating)  
October 18th, 1983

Honorable Commissioner of the Patent Office, Kazuo  
WAKASUGI

1. Identification of the case [stamp:]  
Patent filing no: Sho. 58-57465 OK

2. Title of the Invention

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3. Amending party  
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5. Date of correction order  
Self originating [stamp:]  
Patent Office  
October 19, 1983  
[illegible] section no. 2

6. Object of amendment

Column of the "Detailed Description of the Invention" of  
the specification document.

7. Contents of the amendment

- (1) In line 10 of page 4 within the specification document,  
correct "as a deprotected group of the compound  
indicated by ..." to read "append the reaction of  
deprotection of R<sub>1</sub><sup>a</sup> of the compound indicated by ...".
- (2) In line 9 of page 7 of the same, correct "oximino  
group" to read "oxyimino group".
- (3) In line 12 of the same, erase "reductively".

⑯ 日本国特許庁 (JP)

⑪ 特許出願公開

⑫ 公開特許公報 (A)

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審査請求 未請求

(全 18 頁)

⑭ 新規セフェム化合物

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⑯ 出 願 昭58(1983)4月1日

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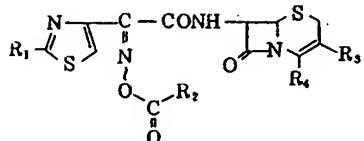
明細書

1. 発明の名称

新規セフェム化合物

2. 特許請求の範囲

1 一般式



[式中、R<sub>1</sub>はアミノ基または保護されたアミノ基、R<sub>2</sub>はC<sub>1</sub>～C<sub>4</sub>の低級アルキル基、R<sub>3</sub>はビニル基、低級アルキルチオ基、-CH=CHCOOR'<sub>1</sub> (R'<sub>1</sub>は水素又は低級アルキル基)又は-CH<sub>2</sub>COOR'<sub>1</sub> (R'<sub>2</sub>は水素又は低級アルキル基)、R<sub>4</sub>はカルボキシル基又は保護されたカルボキシル基を示す]で表わされるセフェム化合物及び医薬品として許容されるその塩類。

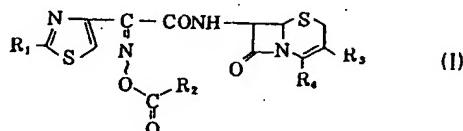
2 特許請求の範囲 第1項記載の化合物のシン異性体。

3. 発明の詳細な説明

本発明は新規なセフェム化合物及びその医薬として許容される塩類に関する。

現在数多くのセファロスボリン系化合物が市販され、臨床に使用されているが、その中で経口投与可能なものはセファレキシン、セファトリジン、セファクロル、セフロキサジン等と数少ない。そこで本発明者らは広範囲の抗菌スペクトルを有ししかも耐性菌に有効かつ経口投与可能なセファロスボリン化合物の探索を意図し、セファロスボリン核の7位及び3位の種々の置換基を検討中に特定のセフェム化合物が広範囲の抗菌力を有し、しかも経口投与による感染治療効果が優れていることを見い出し本発明を完成させた。

すなわち、本発明は優れた抗菌活性を有する新規なセフェム化合物、更に詳しくは、次の一般式(I)

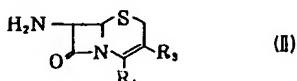


(式中、R<sub>1</sub>はアミノ基または保護されたアミノ基、R<sub>2</sub>はC<sub>1</sub>～C<sub>4</sub>の低級アルキル基、R<sub>3</sub>はビニル基、低級アルキルチオ基、-CH=CHCOOR<sub>3</sub> (R<sub>3</sub>は水素又は低級アルキル基)又は-CH<sub>2</sub>COOR<sub>3</sub> (R<sub>3</sub>は水素又は低級アルキル基)、R<sub>4</sub>はカルボキシル基又は保護されたカルボキシル基を示す)

で表わされるセフエム化合物及び医薬品として許容されるその塩類を提供するものである。

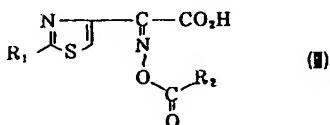
本発明化合物(I)は、例えば次に示す何れかの方法によつて製造される。

① 一般式(B)



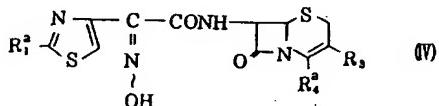
(式中、R<sub>3</sub>及びR<sub>4</sub>は前記と同じ)

で表わされる化合物又はそのN-シリル誘導体に一般式(III)



で表わされる化合物を製造する。

③ 一般式(VI)



(式中、R<sub>4</sub>は保護されたカルボキシル基を示し、R<sub>1</sub>及びR<sub>3</sub>は前記と同じ)

で表わされる化合物に一般式(V)又は(VI)



(式中、Xはハロゲン原子を示し、R<sub>2</sub>は前記と同じ)

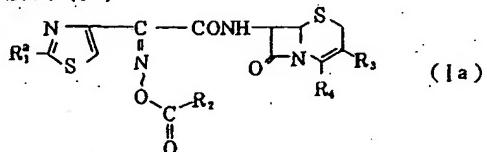
で表わされる化合物を反応させ、次いで要すれば保護基を除去することにより(I)式の本発明化合物を製造する。

上記式(I)～(VI)において、「低級」とは特にことわらない限り炭素数1～4のものを意味する。R<sub>1</sub>で表わされるアミノ保護基としては、所望により脱離できる通常の保護基であればよく、例えば2,2-トリクロロエトキシカルボニル基、2-

(式中、R<sub>1</sub>及びR<sub>2</sub>は前記と同じ)

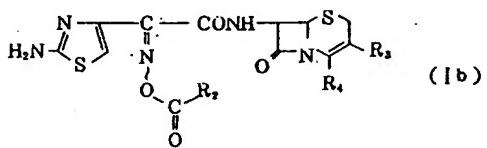
で表わされる化合物又はそのカルボキシル基における反応性誘導体と反応させ、次いで要すれば保護基を除去することにより(I)式の本発明化合物を製造する。

② 一般式(Ia)



(式中、R<sub>1</sub>は保護されたアミノ基を示し、R<sub>2</sub>、R<sub>3</sub>及びR<sub>4</sub>は前記と同じ)

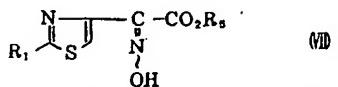
で表わされる化合物を脱保護基として一般式(Ib)



(式中、R<sub>1</sub>、R<sub>3</sub>及びR<sub>4</sub>は前記と同じ)

メチルスルホニルエチルオキシカルボニル基、1-ブロキシカルボニル基、クロロアセチル基、トリチル基等が好適に使用される。R<sub>4</sub>で表わされるカルボキシル保護基としては、β-ラクタム系化合物に通常使用されているものであればよく、例えばジフェニルメチル基、p-ニトロベンジル基、トリクロロエチル基、p-メトキシベンジル基、アリル基等が挙げられる。また、化合物(V)のカルボキシル基における反応性誘導体としては、例えば酸ハロゲン化物、酸アシド、酸無水物、混合酸無水物、活性アミド、活性エステル等が挙げられる。また、化合物(V)及び(VI)のハロゲン原子としては塩素、臭素又はヨウ素が挙げられる。

本発明方法①の原料である(V)式の化合物は、例えば一般式(VII)



(式中、R<sub>3</sub>はカルボキシル保護基を示し、R<sub>1</sub>は前記と同じ)

で表わされる化合物に次式(V)又は(VI)、



(式中、R<sub>2</sub>及びXは前記と同じ)

で表わされる化合物を反応させ、次いでカルボキシル保護基を脱離することにより製造される。

化合物(V)と化合物(VI)又は(VII)との反応は、塩基の存在下有機溶媒、水又は含水溶媒中で行われる。カルボキシル保護基の脱離は、オキシムのアシリ基の開裂分解及びオキシムイミノ基の分解等が生起しない条件で行われなければならない。このためには、R<sub>2</sub>としてアリル基を使用し、バラジウム触媒を用いて還元的に除去する方法(J. Org. Chem. 47-587, 1982年)、R<sub>2</sub>としてt-ブチル基、p-メトキシベンジル基、ジフェニルメチル基を使用し、酸で加水分解する方法が採用される。

本発明方法①において、(V)式の化合物のカルボキシル基における反応性誘導体を使用する場合には、反応は、例えば水、アセトン、ジオキサン、アセトニトリル、クロロホルム、塩化メチレン、

テトラヒドロフラン、酢酸エチル等の反応に悪影響を与えない溶媒中、冰冷下で行うのが好ましい。また、(V)式の化合物を遊離の形で使用するときは、縮合剤の存在下に行うのが好ましい。この縮合剤としては、例えばN,N'-ジシクロヘキシルカルボジイミド; N-シクロヘキシル-N'-モルホリノエチルカルボジイミド; N-シクロヘキシル-N'-(4-ジエチルアミノシクロヘキシル)カルボジイミド; N,N'-ジエチルカルボジイミド; N,N'-ジイソプロピルカルボジイミド; N-エチル-N'-(3-ジメチルアミノプロピル)カルボジイミド; N,N'-カルボニルビス-(2-メチルイミダゾール); ベンタメチレンケテン-N-シクロヘキシルイミン; ジフェニルケテン-N-シクロヘキシルイミン; エトキシアセチレン; 1-アルコキシ-1-クロロエチレン; 亜りん酸トリアルキル; ポリりん酸エチル; ポリりん酸イソプロピル; オキシ塩化りん; 三塩化りん; 塩化チオニル; 塩化オキザリル; トリフェニルホスファイン; 2-エチル-7-ヒドロキシベンズイソキサゾリ

ウム塩; 2-エチル-5-(m-スルホフェニル)イソキサゾリウムヒドロキシド分子内塩; 1-(p-クロロベンゼンスルホニルオキシ)-6-クロロ-1H-ベンゾトリアゾールまたジメチルホルムアミドと塩化チオニル、ホスゲン、オキシ塩化りんなどとの反応によって得られるいわゆるヴィルスマイヤー試薬などが挙げられる。

この反応はまた無機塩基または有機塩基の存在下に行なつてもよく、このような塩基の例としては、炭酸水素アルカリ金属(例えば炭酸水素ナトリウム、炭酸水素カリウムなど)、炭酸アルカリ金属(例えば炭酸ナトリウム、炭酸カリウムなど)、炭酸アルカリ土類金属(例えば炭酸カルシウムなど)、トリ(低級)アルキルアミン(例えばトリメチルアミン、トリエチルアミンなど)、ビリジン、N-(低級)アルキルモルホリン、N,N'-ジ(低級)アルキルベンジルアミンなどが挙げられる。

反応温度は特に限定されず、反応は通常冷却下ないし加温下に行なわれる。

本発明において、目的化合物(I)のシン異性体は化合物(V)と化合物(VI)の対応するシン異性体とを、例えば前記ヴィルスマイヤー試薬の存在下に中性条件で反応させることによつて得ることができる。

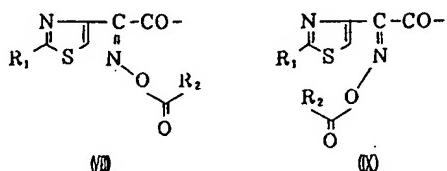
また、本発明方法③の反応は、自体公知の方法によつて行われる。すなわち、化合物(V)と(VI)の反応は、塩化メチレン、酢酸エチル、テトラヒドロフラン等の溶媒中、ビリジン、トリエチルアミン等の有機塩基又は炭酸カリウム、重炭酸ナトリウム等の無機塩基の存在下、-20~20℃の温度で行われる。また化合物(V)と(VI)との反応は、ジメチルホルムアミド、ジメチルスルホキシド等の溶媒中0~5℃の温度で行うのが好ましい。

更にまた、本発明方法①~③の各方法において、保護基の除去は、その種類に応じて公知の方法、例えば酸による加水分解、アルカリによる加水分解、還元等の方法を採用できる。

本発明化合物(I)、(Ia)、(Ib)並びに原料化合物(V)、(VI)、(VII)にはシン異性体とアンチ異性体が存在するが、両異性体及びその混合物の何れも本発明

に含まれる。

ここで、目的化合物(I)において、シン異性体及びアンチ異性体とは、それぞれ次の部分構造體、(Ia)を有する幾何異性体を意味する。



(式中、R<sub>1</sub> 及び R<sub>2</sub> は前記と同じ)

本発明化合物は、遊離カルボキシル基又はノ及び遊離アミノ基を有している場合には、常法によつて医薬として許容される塩類に導くことができる。当該塩類は通常の非毒性の塩であり、そのような塩としてはアルカリ金属塩（例えばナトリウム塩、カリウム塩など）およびアルカリ土類金属塩（例えばカルシウム塩、マグネシウム塩など）のような金属塩、アンモニウム塩、有機塩基との塩（例えばトリメチルアミン塩、トリエチルアミン塩、ピリジン塩、ピコリン塩、ジシクロヘキシ

ルアミン塩、N,N'-ジベンジルエチレンジアミン塩など）、有機酸との塩（例えば酢酸塩、マレイン酸塩、酒石酸塩、メタンスルホン酸塩、ベンゼンスルホン酸塩、琥珀酸塩、トルエンスルホン酸塩など）、無機酸との塩（例えば塩酸塩、臭化水素酸塩、硫酸塩、りん酸塩など）、またはアミノ酸との塩（例えばアルギニン塩、アスパラギン酸塩、グルタミン酸塩など）などが含まれる。

本発明の目的化合物(I)およびその医薬として許容される塩は新規化合物であり、強い抗菌活性を示し、グラム陽性菌及びグラム陰性菌を含む広い範囲の病原性微生物の発育を阻止し、特に経口投与用の抗菌剤として有用である。本発明の目的化合物(I)、またはその医薬として許容される塩を治療の目的で投与するにあたっては、上記化合物を有効成分として含有せしめ、医薬として許容される担体と混合して慣用の製剤の形で投与できる。担体としては、経口投与、非経口投与または外用に適した有機もしくは無機、固体もしくは液体の賦形剤を挙げることができる。また剤形としては、

カプセル剤、錠剤、糖衣錠、軟膏、坐剤、溶液、懸濁液、乳剤などが挙げられる。

次にこの発明で提供される目的化合物の有用性を示すために、本発明の化合物のうち代表的なものについて、抗菌活性を調べた結果を示す。

### 1. 抗菌活性

#### (a) 試験方法

試験は寒天平板希釈法で行ない、第1表に示す各試験菌の増殖が起らなくなる最小発育阻止濃度（MIC）を観察し記録した。結果を第1表に示す。

#### (b) 試験化合物

A : 7-[2-(2-アミノチアゾール-4-イル)-2-アセチルオキシイミノアセトアミド]-3-メチルチオ-3-セフエム-4-カルボン酸トリフロロ酢酸塩（シン異性体）

B : 7-[2-(2-アミノチアゾール-4-イル)-2-ビバロイルオキシイミノアセトアミド]-3-メチルチオ-3-

セフエム-4-カルボン酸トリフロロ酢酸塩（シン異性体）

C : 7-[2-(2-アミノチアゾール-4-イル)-2-プロピオノイルオキシイミノアセトアミド]-3-メチルチオ-3-セフエム-4-カルボン酸トリフロロ酢酸塩（シン異性体）

D : 7-[2-(2-アミノチアゾール-4-イル)-2-イソブチリルオキシイミノアセトアミド]-3-メチルチオ-3-セフエム-4-カルボン酸トリフロロ酢酸塩（シン異性体）

E : 7-[2-(2-アミノチアゾール-4-イル)-2-ビバロイルオキシイミノアセトアミド]-3-エチルチオ-3-セフエム-4-カルボン酸トリフロロ酢酸塩（シン異性体）

F : 7-[2-(2-アミノチアゾール-4-イル)-2-ビバロイルオキシイミノアセトアミド]-3-メトキシカルボニ

ルメチル-3-セフエム-4-カルボン

酸ナトリウム塩

G : 7 - [ 2 - ( 2 - アミノチアゾール - 4  
 - イル ) - 2 - ピバロイルオキシイミノ  
 アセトアミド ] - 3 - ビニル - 3 - セフ  
 エム - 4 - カルボン酸トリフロロ酢酸塩  
 ( シン異性体 )

以下余白

試験菌	試験化合物						
	A	B	C	D	E	F	G
Sta. aureus 606	0.78	1.56	0.78	0.78	25	6.25	1.56
Sta. aureus 606 E 25	0.78	1.56	0.78	0.78	25	3.13	1.56
Sta. aureus 209P JC-1	0.20	0.39	0.20	0.39	6.25	1.56	0.39
Sta. aureus Smith (I)	0.20	0.78	0.20	0.39	1.25	1.56	0.78
Sta. epidermidis ATCC 14990	0.20	0.78	0.20	0.37	6.25	1.56	0.78
B. subtilis ATCC 6633	0.39	0.78	0.39	0.39	1.25	3.13	0.78
E. coli W3630 RGN823	0.78	6.25	0.78	1.56	1.25	1.25	6.25
E. coli W3630 RGN14	0.78	1.25	1.56	3.13	1.25	25	6.25
E. coli W3630 RGN238	1.56	6.25	1.56	1.56	1.25	25	6.25
E. coli ML1410	0.78	1.25	1.56	3.13	1.25	25	1.25
E. coli NIHJ JC-2	0.78	3.13	0.78	1.56	1.25	1.25	6.25
E. coli No.29	0.39	3.13	0.78	0.78	1.25	6.25	3.13
Kleb. pneumoniae GN69	0.39	1.56	0.39	0.78	6.25	6.25	1.56
Kleb. pneumoniae GN118	0.39	3.13	0.39	0.78	6.25	1.25	3.13
Kleb. pneumoniae PC1602	0.78	3.13	0.39	0.78	6.25	1.25	3.13
Pro. mirabilis GN79	1.56	6.25	25	3.13	25	25	3.13
Pro. mirabilis GN310						1.25	25
Sal. typhi O-901-W	0.39	0.78	0.20	0.39	6.25	6.25	0.78

試験菌	試験化合物						
	A	B	C	D	E	F	G
Sal. typhimurium LT-2	0.39	3.13	0.39	0.78	1.25	1.25	1.56
Sal. enteritidis No:11	0.20	0.20	0.10	0.10	6.25	0.78	0.20
Shigella dysenteriae Shigae	0.20	0.78	0.20	0.39	6.25	3.13	0.78
Pro. vulgaris GN76	1.56	6.25	6.25	1.25	5.0	1.25	3.13
Pro. vulgaris GN106	0.78	3.13	1.56	3.13	5.0	1.25	3.13
Pro. vulgaris OX-19						1.25	1.25
Pro. morganii Kōno						2.5	5.0
Pro. rettgeri GN624	0.20	1.56	0.39	0.78	6.25	3.13	3.13
Pro. rettgeri J-0026	0.20	0.78	0.20	0.39	6.25	1.56	1.56
E. coli GN206						6.25	6.25
Citro. freundii GN346/16	1.51	6.25	0.78	1.56	1.25	2.5	6.25
Enter. cloacae G-0005						5.0	1.25
Enter. cloacae G-0008			6.25	6.25	2.5	2.5	6.25
Serr. marcescens No.1	1.51	6.25	3.13	3.13	2.5	2.5	6.25
Serr. marcescens No.2	3.13		3.13	3.13	2.5	5.0	1.25
Ps. cepacia M-0527	1.56	1.25	3.13	3.13	1.25	1.25	1.25
Str. faecalis W-75					1.25		

## 2. 感染治療実験

## (a) 試験方法

試験は供試動物として、ICR-JCL系マウス（4週令雄、体重 $20 \pm 0.5$ g）のものを1群3匹として用いた。感染に用いた菌株はエシユリヒア・コリ（Escherichia Coli）No 29であり、これをheart infusion agarにて37°C、20時間前培養後、生理食塩水にて懸濁し、mucinを2.5%濃度になるよう混合した後、マウス腹腔内に注入した。薬剤サンプルは種々の濃度を菌感染直後に経口投与し、7日後のマウス生存数を観察した。結果を第2表に示す。

## (b) 試験化合物

H : 7 - [ 2 - ( 2 - アミノチアゾール - 4 - イル ) - 2 - アセチルオキシイミノアセトアミド ] - 3 - メチルチオ - 3 - セフエム - 4 - カルボン酸ビパロイルオキシメチルエステル（シン異性体）

I : 7 - [ 2 - ( 2 - アミノチアゾール - 4 - イル ) - 2 - ヒドロキシイミノアセテート（シン異

-イル ) - 2 - ビパロイルオキシイミノアセトアミド ] - 3 - メチルチオ - 3 - セフエム - 4 - カルボン酸ビパロイルオキシメチルエステル（シン異性体）

第2表

投与量 (mg/マウス)	生存率						
	A*	B*	E*	H	I	セフロキサジン	無治療对照群
1.0	3/3	3/3	3/3	3/3	3/3	3/3	0/3
1	3/3	3/3	3/3	3/3	3/3	2/3	0/3
0.1	0/3	2/3	2/3	2/3	2/3	0/3	0/3

\* 試験化合物A、B及びEは前記と同じ。

つぎに本発明を参考例及び実施例により詳細に説明するが、本発明はこれら実施例により限定されるものではない。

## 参考例 1

エチル - 2 - ( 2 - アミノチアゾール - 4 - イル ) - 2 - ヒドロキシイミノアセテート（シン異

性体) :

冰酢酸 3.0 ml 中におけるアセト酢酸エチル 3.0 g の溶液を搅拌し氷冷する。これに反応温度が 10 °C 以下に維持される様な速度で、水 4.0 ml 中における亜硝酸ナトリウム 1.8 g の溶液を加えた。約 3.0 分間氷冷下搅拌し、ついで水 8.0 ml 中における塩化カリウム 1.6 g の溶液を加えた。生成する混合物を 1 時間搅拌した。下層の有機層を分離し、そして水層をジエチルエーテルで抽出した。抽出物を油状物と合一し、水、飽和食塩水で順次洗浄し、乾燥させ濃縮乾固し、エチル-2-ヒドロキシイミノ-3-オキソブチレート(シン異性体) 3.0 g を得た。塩化メチレン 4.0 ml 中エチル-2-ヒドロキシイミノ-3-オキソブチレート(シン異性体) 1.5 g の溶液を搅拌しそして氷冷する。これにスルフリルクロライド 1.4 g を滴下し、2 日間搅拌した。水洗した後、乾燥し濃縮した。残留油状物 1.7 g をエタノール 5.0 ml 中に溶解し、そしてジメチルアニリン 7.7 ml、及びチオ尿素 4.2 g を搅拌しながら加えた。2 時間後に生成物を沪

取しエタノールで洗净し乾燥し表記化合物 7.8 g 得た。

mp 188 °C (分解)

参考例 2

エチル-2-(2-トリチルアミノチアゾール-4-イル)-2-ヒドロキシイミノアセテート塩酸塩(シン異性体) :

トリエチルアミン 8.4 ml 含有ジメチルホルムアミド 3.0 ml 中における参考例 1 の生成物 1.3 g の溶液を搅拌、冷却(-30 °C)し、これに 2 時間かけてトリチルクロライド 16.75 g を加えた。混合物を同温度で 3.0 分間搅拌後、室温で 1.7 時間搅拌した。

次に水 500 ml と酢酸エチル 500 ml との間に分配した。有機層を分離し水で洗净しついで 1 N-HCl 500 ml で搅拌した。析出する沈殿を築め、水、酢酸エチル、及びエーテルで順次洗净し乾燥した。表記化合物を白色固体として 1.6.4 g 得た。

mp 184 ~ 186 °C (分解)

参考例 3

2-(2-トリチルアミノチアゾール-4-イル)-2-ヒドロキシイミノ酢酸ナトリウム塩(シン異性体) :

2-(2-トリチルアミノチアゾール-4-イル)-2-ヒドロキシイミノ酢酸エチル・塩酸塩(シン異性体) 2.0 g をエタノール 4.0 ml に懸濁し、氷冷下 1 N-NaOH 水溶液 4.0 ml を滴下する。室温下、2.4 時間搅拌後、析出する沈殿を沪取する。沈殿物をエーテルで洗净後、テトラヒドロフラン 5.0 ml に懸濁し、氷冷下 1.0 % HCl で pH = 2.0 に調整して、均一溶液を得る。次に氷冷下飽和重ソウ水で pH = 8.0 に調整すると沈殿が析出する。沪取し水、エーテルで順次洗净後乾燥する。白色粉末 1.6 g 得る。

参考例 4

2-(2-トリチルアミノチアゾール-4-イル)-2-ヒドロキシイミノ酢酸アリルエステル(シン異性体) :

2-(2-トリチルアミノチアゾール-4-イル)-2-ヒドロキシイミノ酢酸アリルエステル(シン異性体) 4.69 g を乾燥塩化メチレン 1.0 ml に溶解し、氷冷下ピリジン 0.1 ml を加える。次

ル)-2-ヒドロキシイミノ酢酸ナトリウム塩 1.8 g をジメチルホルムアミド 2.0 ml に溶解し、これに氷冷下アリルアイオダイド 0.8 ml を加え、室温下 2.4 時間搅拌する。該反応液を酢酸エチル 200 ml - 水 2.0 ml の混液に加え、有機層を水洗する(200 ml × 2)。硫酸マグネシウムで乾燥後濃縮乾固し、このものを和光ゲル C-200 6.0 g で精製する(采:トルエン-酢酸エチル)。収量 1.3 g。

NMR (80 MHz, δ 値, PPM, CDCl<sub>3</sub>) :

4.85 (2H, m), 5.25 ~ 5.50 (2H, m), 5.95 (1H, m), 6.90 (1H, s), 7.85 (16H, b.s)

参考例 5

2-(2-トリチルアミノチアゾール-4-イル)-2-アセチルオキシイミノ酢酸アリルエステル(シン異性体) :

2-(2-トリチルアミノチアゾール-4-イル)-2-ヒドロキシイミノ酢酸アリルエステル(シン異性体) 4.69 g を乾燥塩化メチレン 1.0 ml に溶解し、氷冷下ピリジン 0.1 ml を加える。次

にアセチルクロライド 0.1 ml を含む乾燥塩化メチレン 1 ml を滴下し、同温度で 20 分間攪拌する。水洗し硫酸マグネシウムで乾燥する。濃縮乾固後シリカゲルで精製し目的物 500 mg 得る。

FD mass ; 511

IR (ヌジョール) ; 3300, 1740 cm<sup>-1</sup>

NMR (80 MHz, δ 値, PPM) :

2.11 (3H, s), 4.75~4.85 (2H, m), 5.20~5.48 (2H, m), 5.70~6.15 (1H, m), 6.85 (1H, s), 7.80 (15H, s)

参考例 5 と同様にして、2-(2-トリチルアミノチアゾール-4-イル)-2-ヒドロキシイミノ酢酸アリルエステル（シン異性体）を対応する酸クロライドと反応させて、次の参考例 6～8 の化合物を得た。

#### 参考例 6

2-(2-トリチルアミノチアゾール-4-イル)-2-プロピノイルオキシイミノ酢酸アリルエステル（シン異性体）：

FD mass ; 525

FD mass ; 553

IR (ヌジョール) ; 3300, 1740 cm<sup>-1</sup>

NMR (80 MHz, δ 値, PPM) :

1.25 (9H, s), 4.70~4.85 (2H, m), 5.16~5.55 (2H, m), 5.65~6.20 (1H, m), 6.90 (1H, s), 7.26 (16H, s)

#### 参考例 9

2-(2-トリチルアミノチアゾール-4-イル)-2-アセチルオキシイミノ酢酸（シン異性体）：

2-(2-トリチルアミノチアゾール-4-イル)-2-アセチルオキシイミノ酢酸アリルエ斯特ル（シン異性体）250 mg を乾燥塩化メチレン 1.0 ml に溶解し、これに氷冷下 2-エチルヘキサン酸カリウム 85 mg を含む酢酸エチル溶液 5 ml、更にトリフェニルホスフィン 1.2 mg 及びテトラキストリフェニルホスフィンパラジウム (0) 1.2 mg を加え、同温度で 1 時間攪拌する。次いで析出する沈殿を戻りし、イソプロピルエーテル、酢酸エチルで順次洗浄し乾燥して 2-(2-トリチルアミ

IR (ヌジョール) ; 3300, 1740 cm<sup>-1</sup>

NMR (80 MHz, δ 値, PPM) :

1.25 (3H, t, J=8Hz), 2.5 (2H, q, J=8Hz), 4.75~4.85 (2H, m), 5.20~5.48 (2H, m), 5.70~6.15 (1H, m), 6.82 (1H, s), 7.80 (15H, b.s.)

#### 参考例 7

2-(2-トリチルアミノチアゾール-4-イル)-2-イソブチリルオキシイミノ酢酸アリルエ斯特ル（シン異性体）：

FD mass ; 540

IR (ヌジョール) ; 3300, 1745 cm<sup>-1</sup>

NMR (80 MHz, δ 値, PPM) :

1.20 (6H, d, J=8Hz), 2.60 (1H, m), 4.70~4.82 (2H, m), 5.15~5.48 (2H, m), 5.70~6.15 (1H, m), 6.85 (1H, s), 7.20 (16H, s)

#### 参考例 8

2-(2-トリチルアミノチアゾール-4-イル)-2-ビバロイルオキシイミノ酢酸アリルエ斯特ル（シン異性体）：

ノチアゾール-4-イル)-2-アセチルオキシイミノ酢酸カリウム塩を得る。ここで得たカリウム塩を酢酸エチル 2.0 ml に懸濁し、氷冷下 5% HCl 溶液で pH = 2.0 に調整する。飽和食塩水で洗浄し乾燥する。濃縮乾固し目的生成物を白色粉末として 130 mg 得る。

NMR (80 MHz, δ 値) :

2.15 (3H, s), 6.80 (1H, s), 7.30 (16H, b.s.)

参考例 9 と同様にして、対応する 2-(2-トリチルアミノチアゾール-4-イル)-2-アルキルアシルオキシイミノ酢酸アリルエ斯特ル（シン異性体）を原料とし、パラジウム触媒の存在下 2-エチルヘキサン酸カリウムを用いて次の参考例 10～12 の化合物を得た。

#### 参考例 10

2-(2-トリチルアミノチアゾール-4-イル)-2-プロピオノイルオキシイミノ酢酸：

NMR (80 MHz, δ 値, PPM, CDCl<sub>3</sub>) :

1.25 (3H, t, J=8Hz), 2.5 (2H, q, J=8Hz), 6.80 (1H, s), 7.30 (16H, b.s.)

## 参考例 1 1

2-(2-トリチルアミノチアゾール-4-イル)-2-イソブチリルオキシイミノ酢酸：

NMR (80 MHz, δ 値, ppm, CDCl<sub>3</sub>) ;  
1.05 (6H, d, J=8 Hz), 2.40 (1H, m), 6.85  
(1H, s), 7.30 (16H, b.s.)

## 参考例 1 2

2-(2-トリチルアミノチアゾール-4-イル)-2-ビパロイルオキシイミノ酢酸：

NMR (80 MHz, δ 値, ppm, CDCl<sub>3</sub>) ;  
1.16 (9H, s), 6.80 (1H, s), 7.28 (16H, b.s.)

## 参考例 1 3

7-β-フエニルアセタミド-3-メチルチオ-3-セフエム-4-カルボン酸-p-ニトロベンジルエステル：

乾燥アセトニトリル 4.0 mL、7-β-フエニルアセタミド-3-ヒドロキシ-3-セフエム-4-カルボン酸-p-ニトロベンジルエステル 5.6 g (12 mM) を懸濁させ、攪拌しながら窒素雰囲気下-20°Cに冷却し、ジイソプロピル-エチ

5H, s), 7.63, 8.20 (4H, 2×d, (J=8.2)),  
8.83 (1H, d, (J=7.8))。

## 参考例 1 4

7-フエニルアセタミド-3-メチルチオ-3-セフエム-4-カルボン酸：

7-フエニルアセタミド-3-メチルチオ-3-セフエム-4-カルボン酸-p-ニトロベンジルエステル [mp. 231°C (分解)] 2.5 g をジオキサン 1.5 mL、85% ギ酸 1.0 mL に加え、5.0 ~ 5.5°C に加温し、攪拌下に亜鉛末 1.5 ~ 3 g を数回に分けて加え、2 ~ 5 時間反応させる。薄層クロマトグラフィ (TLC) で反応終了を確認した後、室温に冷し、不溶物を築め、ジオキサンで洗う。反応液と洗液を合わせ、減圧で溶媒の大部分を留去する。酢酸エチル 1.0 mL、氷水 5.0 mL 中に攪拌しながら、酸性炭酸ナトリウム液で pH 7.0 ~ 7.5 に調整しつつ、反応液を少量づつ滴下する。全量添加後、不溶物を築め水洗する。水層および洗液を合わせ、酢酸エチルで数回抽出する。有機層は少量の水で水洗し、水層を合わせ、必要があ

ルアミン 2.4 mL 及びジフェニル-クロロホスフエート 2.8 mL を加えた。反応混合物を約 30 分間同温度で攪拌し、透明溶液を得た。TLC で反応終了を確認後、反応液を -30°C に冷却し、ジイソプロピル-エチルアミン 2.4 mL を加え、メチルメルカプタン約 3 g を攪拌下に吹込んだ。-25 ~ -30°C で約 2 時間攪拌しながら反応を続け (結晶析出)、TLC で反応終了を確認した後、酢酸 0.5 mL を加えた。

生成物を築め、冷アセトニトリル 7 mL、イソプロピルエーテル 1.0 mL で順次洗净後、真空乾燥した。収量：4.95 g (収率：83%)。

mp : 231°C (分解)

IR (ヌジョール) ; 3230, 1775 (β-ラクタム),  
1705, 1650 cm<sup>-1</sup>

UV λ<sub>max</sub> ; 319 nm

NMR (DMSO-d<sub>6</sub> + CDCl<sub>3</sub>) ; δ 値 (60 MHz)  
3.28 (3H, s), 3.61 (2H, s), 3.68 (2H, s),  
5.03 (1H, d, (J=4.6 Hz)), 5.73 (2H, s),  
5.64 (1H, dd, (J=4.6, J=7.8 Hz)), 7.29 (

れば、活性炭処理をする。水層は塩酸で pH 1 ~ 2 に調整し、一夜冰室におく。固形物を築め、水洗後、少量のイソプロピルエーテルで洗い乾燥して、標題の化合物を得た。収量：1.4 g (77%)。アセトン+イソプロピルエーテルから再結晶。

mp 197 ~ 198°C (分解)

UV λ<sub>max</sub> ; 318 nm (95% エタノール)  
IR (ヌジョール) ; 3280 (NH), 1770 (β-ラクタム), 1690, 1640 cm<sup>-1</sup>

NMR (DMSO-d<sub>6</sub> + CDCl<sub>3</sub>) ; δ 値 [60 MHz (R600)]  
2.33 (3H, s), 3.57 (2H, s), 3.67 (2H, s),  
5.01 (1H, d, J=4.7 Hz), 5.56 (1H, dd, J=4.7, 8.2 Hz), 7.25 (5H, s), 9.01 (1H, d, J=8.2 Hz)

## 参考例 1 5

7-フエニルアセタミド-3-メチルチオ-3-セフエム-4-カルボン酸ジフェニルメチルエステル：

参考例 1 4 で得られた 7-フエニルアセタミド-3-メチルチオ-3-セフエム-4-カルボン

酸 1.8 2 g をアセトンに温めて溶かす。搅拌しながらジアゾジフェニルメタンの n - ヘキサン溶液を加える。TLCで反応を追跡しながら室温で一夜反応させた後、減圧濃縮し乾固する。過剰のジアゾジフェニルメタンを n - ヘキサンで処理して除く。固体物を塩化メチレンに溶し、酸性炭酸ソーダ水で pH 7.5 に調整した。塩化メチレン層を分取し、乾燥後減圧濃縮乾固し、固体物をイソブロピルエーテル、エチルエーテルで処理して乾燥し、標題の化合物を得た。収量： 2.4 g (90%)。アセトン + メタノールから再結晶。

mp 162 ~ 163 °C (分解)

UV  $\lambda_{\text{max}}$  : 318 nm (95% エタノール)  
IR (ヌジョール) : 3230 (NH), 1780 ( $\beta$ -ラクタム), 1700 (エステル),  
 $1650 \text{ cm}^{-1}$

NMR (CDCl<sub>3</sub>) : δ 値 (60 MHz)

1.99 (3H, s), 2.91, 3.38 (2H, ABq, J = 16.8 Hz), 3.64 (2H, s), 4.95 (1H, d, J = 4.3 Hz), 5.62 (1H, d, d, J = 4.3, 8.6 Hz).

6.86 (1H, s), 7.2 ~ 7.33 (16H)

#### 参考例 1-6

7-アミノ-3-メチルチオ-3-セフエム-4-カルボン酸ジフェニルメチルエステル塩酸塩：

参考例 1-5 で得られた 7-フェニルアセタミド-3-メチルチオ-3-セフエム-4-カルボン酸ジフェニルメチルエステル 2.65 g を塩化メチレン 5.0 ml に溶かし、-30 °C に冷す。これに無水ビリジン 4 ml を加え、さらに五塩化リンの微粉末 3.2 g を投入する。徐々に昇温させ、-10 ~ 10 °C で約 3 時間搅拌する。TLC で反応終了を確かめた後、-40 °C に冷す。(反応液の一部を取り、無水メタノールを加え、ベンゼン : 酢酸エチル = 2 : 1 で展開する。) この反応液 (結晶析出) に搅拌下、無水メタノール 1.5 ml を滴下する。透明な反応液は、徐々に昇温させ、-10 °C で約 1 時間搅拌する。TLC で反応終了を確かめた後、4.0 ml の冷食塩水中に加え、搅拌下、希アンモニア水で pH 1.5 ~ 2.0 に保ちながら氷冷下約 1 時間反応させる。析出物を集め、少量の冰水、酢酸

エチル、イソブロピルエーテルの順に洗い、乾燥して標題の化合物を得た。収量： 2.25 g (91%)。

mp 203 ~ 205 °C (分解)

UV  $\lambda_{\text{max}}$  : 319 nm (95% エタノール)  
IR (ヌジョール) : 1780 ( $\beta$ -ラクタム),  
 $1760, 1700 \text{ cm}^{-1}$

NMR (DMSO-d<sub>6</sub>) : δ 値 (60 MHz)

2.44 (3H, s), 3.73, 4.13 (2H, ABq, J = 16 Hz), 5.08 (1H, d, J = 4.3 Hz), 5.28 (1H, d, J = 4.3 Hz), 6.90 (1H, s), 7.20 ~ 7.80 (13H, m)

#### 参考例 1-7

7-アミノ-3-エチルチオ-3-セフエム-4-カルボン酸ベンズヒドリルエステル塩酸塩：

参考例 1-3 ~ 1-6 に準じて表記化合物を得た。

mp 172 ~ 173 °C (分解)

UV  $\lambda_{\text{max}}$  : 319 nm (95% エタノール)

IR (ヌジョール) : 1778, 1705  $\text{cm}^{-1}$

NMR (DMSO-d<sub>6</sub>) : δ 値 (60 MHz)

1.16 (3H, t, J = 7 Hz), 2.93 (2H, q, J = 7

Hz), 2.93 (2H, q, J = 7 Hz), 3.68, 4.10 (2H, ABq, J = 15 Hz), 5.05 (1H, d, J = 5 Hz), 5.77 (1H, d, J = 5 Hz), 6.83 (1H, s), 7.3 (10H, m)

#### 参考例 1-8

7-フェニルアセトアミド-3-ビニル-3-セフエム-4-カルボン酸ジフェニルメチルエス

テル：

7-フェニルアセトアミド-3-ブロムメチル-3-セフエム-4-カルボン酸ジフェニルメチルエステル 1.2 g をジメチルホルムアミド 2 ml に溶解し、これにトリフェニルホスファイン 8.18 mg 及びヨウ化ナトリウム 3.11 mg を加え、0 ~ 5 °C で 1 ~ 7 時間搅拌する。反応液をイソブロピルエーテルで洗净して粉末化し、更に酢酸エチルで洗净する。得られた粉末を塩化メチレン 3.0 ml に懸濁し、これに氷冷下 3.6% ホルムアルデヒド溶液 15 ml を加える。次いで飽和炭酸水素ナトリウム水溶液で pH = 9.0 に調整し、氷冷下 30 分、室温で 2 時間搅拌する。更に氷冷下 5% HCl で pH = 5.0 に

調整し塩化メチレンで抽出する。水洗後、硫酸マグネシウムで乾燥する。濾絞乾固しシリカゲルクロマトで精製する。(和光グルC-200-40%、系トルエン酢酸エチル)目的物420mgを得る。

IR(ヌジョール): 1765, 1710 cm<sup>-1</sup>

NMR(80 MHz, δ 値, PPM, CDCl<sub>3</sub>):

3.30, 3.60(2H, ABq, J=19 Hz), 3.56(2H, s), 4.91(1H, d, J=4.8 Hz), 5.16(1H, d, J=8 Hz), 5.36(1H, d, J=15 Hz), 5.75(1H, d, d, J=4.8, 9.0 Hz), 6.25(1H, d, J=9.0 Hz) 6.89(1H, s), 7.10~7.55(16H, m)

#### 参考例 19

7-アミノ-3-ビニル-3-セフエム-4-カルボン酸ジフェニルメチルエステル塩酸塩:  
7-フェニルアセトアミド-3-ビニル-3-セフエム-4-カルボン酸ベンズヒドリルエステル230mgを乾燥塩化メチレン10mlに溶解し-40℃に冷却する。これにビリジン0.36ml及び五塩化リン282mgを加え-40℃で2時間、

0℃で2時間攪拌する。次いで-50℃に冷却し、乾燥メタノール1mlを加え、-50℃で2時間、0℃で1時間攪拌する。反応液に氷冷下飽和食塩水10mlを加え0℃~5℃で30分間攪拌する。これにイソプロピルエーテル20mlを加え析出する沈殿を汎取する。イソプロピルエーテル、酢酸エチルで順次洗浄し目的物164mgを得る。

IR(ヌジョール): 1760, 1705 cm<sup>-1</sup>

NMR(60 MHz, δ 値, PPM, DMSO-d<sub>6</sub>):

3.73, 4.00(2H, ABq, J=18 Hz), 5.1~5.4(2H, m), 5.58(1H, d, J=6 Hz), 5.93(1H, m), 6.97(1H, s), 7.00(1H, d, d, J=12, 18 Hz), 7.42(10H, m), 9.17(2H, m)

#### 参考例 20

7-アミノ-3メチルチオ-3-セフエム-4-カルボン酸エトキシカルボニルオキシエチル塩酸塩(α型):

7-フェニルアセタミド-3-メチルチオ-3-セフエム-4-カルボン酸エトキシカルボニルオキシエチル(α型)(mp 157~158℃)

481mg(0.001モル)を塩化メチレン20mlに溶かし、ビリジン0.40mlを加え-20℃に冷す。これに五塩化リン440mgを加え攪拌下徐々に昇温させ+5~+10℃で約90分反応させる(五塩化リンの消失後30分反応)。反応液を-30℃に冷し、攪拌下イソブタノール2.0mlの塩化メチレン5ml液を滴下する。ついで徐々に昇温させ、+5~+10℃で2時間反応させた(TLCで反応を追跡する)。反応終了後0℃に冷し、食塩水2mlを含む冷水5ml中に攪拌下そそぐ。氷冷下約60分攪拌し、これにジイソプロピルエーテル10ml、エチルエーテル10mlを加えた。まもなく白色晶析出が増えた。この結晶を集め、ジイソプロピルエーテル、エーテルで洗い乾燥した。収量360mg。

mp 148~50℃(分解)

UV λ<sub>max</sub>: 320 nm (95%エタノール)

IR(ヌジョール): 1781, 1762, 1700 cm<sup>-1</sup>

#### 参考例 21

7-アミノ-3-エチルチオ-3-セフエム-

4-カルボン酸-エトキシカルボニルオキシエチルエステル塩酸塩:

7-フェニルアセタミド-3-エチルチオ-3-セフエム-4-カルボン酸エトキシカルボニルオキシエチルエステル(mp 130~31℃)

990mg(0.002モル)を用い、他は参考例20と同様に反応させ処理した。標題の化合物を750mg(90.8%)得た。

mp 188~90℃(分解)

UV λ<sub>max</sub>: 320 nm (95%エタノール)

IR(ヌジョール): 1780, 1763, 1710 cm<sup>-1</sup>

#### 参考例 22

7-フェニルアセトアミド-3-メトキシカルボニルメチル-3-セフエム-4-カルボン酸p-ニトロベンジルエステル:

7-フェニルアセトアミド-3-ヒドロキシ-3-セフエム-4-カルボン酸 p-ニトロベンジルエステル4.7gをジメチルホルムアミド35mlに溶解し、これにカルボメトキシメチレントリフェニルホスホラン4gを加え室温で24時間攪

拌する。反応液を濃縮し、酢酸エチル 500 ml に溶解し、冷 5% HCl、水、飽和食塩水で順次洗浄し硫酸マグネシウムで乾燥する。次いで減圧下濃縮乾固し、残渣を和光グル C-200 (200 g) でカラムクロマト精製する（系：トルエン-酢酸エチル）目的物 28 g を得る。

IR(ヌジョール): 3300, 1760 cm<sup>-1</sup>

NMR(80 MHz, δ 値, ppm, CDCl<sub>3</sub>)

3.20~3.75 (9H, m), 5.00 (1H, d, J=4.8 Hz),  
5.30 (2H, b.s), 5.85 (1H, d.d, J=4.8 Hz,  
9 Hz), 6.15 (1H, d, J=9 Hz), 7.35 (5H, s),  
7.55, 8.22 (4H, ABq, J=9 Hz)

上記反応中、副産物（セフアロスボリン核二重結合の異性体）88.2 mg を得た。この物は常法により過酸で酸化し三塩化リンで還元すると表記目的物と同一物性の物質となつた。

#### 参考例 2 3

7-フェニルアセトアミド-3-メトキシカルボニルメチル-3-セフエム-4-カルボン酸ジフェニルメチルエステル：

5.80 (1H, d, d, J=4.8 Hz, 9.6 Hz), 6.10 (1H, d, J=9.6 Hz), 6.85 (1H, s), 7.15~7.35 (16H, m)

#### 参考例 2 4

7-アミノ-3-メトキシカルボニルメチル-3-セフエム-4-カルボン酸ジフェニルメチルエ斯特ル：

五塩化リン 1.12 g を塩化メチレン 20 ml に溶解し、氷冷下ビリジン 1.45 ml を加える。同温度で 30 分間攪拌し -50 ℃ に冷却する。次いで 7-フェニルアセトアミド-3-メトキシカルボニルメチル-4-カルボン酸ジフェニルメチルエ斯特ル 1.0 g を含む塩化メチレン 10 ml を加え -50 ℃ にて 2 時間、氷冷下にて 2 時間攪拌する。-50 ℃ にて冷却し、乾燥メタノール 4 ml を滴下する。0 ℃ で 1 時間攪拌して氷冷下 20 ml の飽和食塩水を加え同温度で 30 分攪拌する。塩化メチレンで抽出し飽和食塩水で洗浄後氷冷下炭酸水素ナトリウム水で pH = 7.0 に調整する。乾燥後濃縮乾固し和光グル C-200 15 g で精製する（系：ト

7-フェニルアセトアミド-3-メトキシカルボニルメチル-3-セフエム-4-カルボン酸 p-ニトロベンジルエステル 2.8 g をギ酸 50 ml 及びエタノール 50 ml 中に氷冷下に溶解する。攪拌下、亜鉛粉 1.8 g を 10 分間かけて加える。室温で 1 時間、50 ℃ で 2 時間攪拌し不溶物を汎取する。汎液を減圧下に濃縮し酢酸エチル 50 ml - 水 20 ml の混液に加える。氷冷下飽和炭酸水素ナトリウム水で pH = 7.0 に保つ。不溶物を除去し水層を酢酸エチルで洗浄する。水層を 5% HCl で氷冷下 pH = 2.0 に調整し、酢酸エチルで抽出する。

有機層にジフェニルジアゾメタン-ヨウヘキサン溶液を加え室温で反応させる。原料（カルボン酸）が消失したら減圧下濃縮乾固し、残渣をイソプロピルエーテルで洗浄し、目的物 1.27 g を得る。

IR(ヌジョール): 3320, 1770 cm<sup>-1</sup>

NMR(80 MHz, δ 値, CDCl<sub>3</sub>):

3.32~3.70 (9H, m), 4.95 (1H, d, J=4.8 Hz).

ルエン-酢酸エチル）目的物 35.0 mg を得る。

IR(ヌジョール): 1780 cm<sup>-1</sup>

NMR(80 MHz, δ 値, CDCl<sub>3</sub>):

1.70 (2H, b.s), 3.36~3.65 (7H, m), 4.70 (1H, d, J=4.8 Hz), 4.96 (1H, d, J=4.8 Hz), 6.90 (1H, s), 7.20~7.40 (10H, m)

#### 参考例 2 5

7-フェニルアセトアミド-3-メトキシカルボニルビニル-3-セフエム-4-カルボン酸ジフェニルメチルエ斯特ル：

7-フェニルアセトアミド-3-ブロムメチル-3-セフエム-4-カルボン酸ジフェニルメチルエ斯特ル 1.2 g をジメチルホルムアミド 2 ml に溶解し、これにトリフェニルホスファイン 81.8 mg 及びヨウ化ナトリウム 31.1 mg を加え、5 ℃ で 20 時間攪拌する。減圧下濃縮しイソプロピルエーテルで粉末化し、更に酢酸エチルで洗浄する。

得られた塩を塩化メチレン 30 ml に溶解し、これにメチルグリオキザレート・一水和物 58.0 mg を加え、氷冷下飽和炭酸水素ナトリウム水で pH

= 9 に調整し、室温で4時間搅拌する。次いで、氷冷下5%塩酸水でpH = 5.0に調整し塩化メチレンで抽出する。水洗後硫酸マグネシウムで乾燥し濃縮乾固する。和光グルC-200 20gで精製(系:トルエン-酢酸エチル)し、目的物184mgを得た。

IR(ヌジョール): 1780 cm<sup>-1</sup>

NMR(80 MHz, δ値, PPM, CDCl<sub>3</sub>):

3.40~3.65(7H, m), 5.0(1H, d, J=4.2Hz),  
6.70(1H, d, J=12Hz), 6.8(1H, d, d, J=  
4.2Hz, 9.6Hz), 6.15(1H, d, J=9.6Hz),  
6.80(1H, s), 6.82(1H, d, J=12Hz), 7.20  
~7.40(16H, m)

#### 参考例26

7-アミノ-3-メトキシカルボニルビニル-3-セフエム-4-カルボン酸ジフェニルメチルエステル:

窒素気流下、五塩化リン164mgを塩化メチレン2mLに溶解し、これに氷冷下ビリジン0.21mLを加え、同温度で30分搅拌する。他方7-フェ

d, J=12Hz), 6.90(1H, s), 7.2~7.4(10H,  
m)

#### 実施例1

7-[2-(2-トリチルアミノチアゾール-4-イル)-2-ビバロイルオキシイミノアセトアミド]-3-ビニル-3-セフエム-4-カルボン酸ジフェニルメチルエステル(シン異性体):

2-(2-トリチルアミノチアゾール-4-イル)-2-ビバロイルオキシイミノ酢酸(シン異性体)192mg、7-アミノ-3-ビニル-3-セフエム-4-カルボン酸ジフェニルメチルエステル120mg、及び1-ヒドロキシベンズトリアゾール50mgを塩化メチレン10mLに溶解し氷冷する。ジシクロヘキシルカルボジイミド75mgを含む塩化メチレン1mLを加え5℃で終夜搅拌する。減圧下濃縮し、酢酸エチル50mLに溶解する。不溶物を除去し冷5%塩酸水、飽和食塩水で順次洗净する。硫酸マグネシウムで乾燥後、減圧下濃縮乾固する。和光グルC-200 8g(系:トルエン-酢酸エチル)で精製し目的物200mgを得た。

ニルアセトアミド-3-メトキシカルボニルビニル-3-セフエム-4-カルボン酸ジフェニルメチルエステル150mgを含む塩化メチレン1.5mLを先に調製した溶液中に-50℃で滴下する(約10分間)。-50℃で30分間、0~5℃で2時間搅拌後-50℃に冷却し、反応液を-50℃に冷却したメタノール2mL中に滴加する。次いで-50℃で30分間、0~5℃で1時間搅拌後、飽和食塩水3mLを加え、同温度で30分搅拌する。塩化メチレンで抽出し飽和食塩水で洗净する。飽和食塩水の存在下2%炭酸水素ナトリウム水でpH = 7.0に調整し水洗する。硫酸マグネシウムで乾燥し濃縮乾固する。和光グルC-200 2gで精製(系:トルエン-酢酸エチル)し、目的物73mgを得た。

IR(ヌジョール): 1780 cm<sup>-1</sup>

NMR(80 MHz, δ値, PPM, CDCl<sub>3</sub>):

1.75(2H, b.s), 3.40(2H, b.s), 3.56(3H,  
s), 4.7(1H, d, J=4.2Hz), 4.9(1H, d, J=  
4.8Hz), 5.75(1H, d, J=12Hz), 6.85(1H,

IR(ヌジョール): 1770, 1740~1710 cm<sup>-1</sup>

NMR(80 MHz, δ値, PPM, CDCl<sub>3</sub>):

1.30(9H, s), 3.50(2H, b.s), 5.05(1H, d,  
J=5Hz), 5.20(1H, d, J=8Hz), 5.40(1H,  
d, J=14.5Hz), 5.90(1H, d, d, J=5Hz, J=  
9.5Hz), 6.90(2H, b.s), 6.65~7.10(1H, m),  
7.15~7.40(26H, m)

#### 実施例2

7-[2-(2-トリチルアミノチアゾール-4-イル)-2-アセチルオキシイミノアセトアミド]-3-ビニル-3-セフエム-4-カルボン酸ジフェニルメチルエ斯特ル(シン異性体):

実施例1と同様にして、2-(2-トリチルアミノチアゾール-4-イル)-2-アセチルオキシイミノ酢酸を原料として標記化合物を得た。

IR(ヌジョール): 3300, 1770 cm<sup>-1</sup>

NMR(80 MHz, δ値, PPM, CDCl<sub>3</sub>):

2.70(3H, s), 5.0(1H, d, J=4.8Hz), 5.2(1H, d, J=10Hz), 5.4(1H, d, J=16Hz),  
5.8(1H, d, d, J=4.8Hz, J=9.0Hz), 6.8(1H,

s), 6.9 (1H, s), 7.1~7.3 (27H, m)

## 実施例3

7-[2-(2-アミノチアゾール-4-イル)-2-ビバロイルオキシイミノアセトアミド]-3-ビニル-3-セフエム-4-カルボン酸トリフロロ酢酸塩(シン異性体):

7-[2-(2-トリチルアミノチアゾール-4-イル)-2-ビバロイルオキシイミノアセトアミド]-3-ビニル-3-セフエム-4-カルボン酸ジフェニルメチルエステル(シン異性体)200mgをアニソール0.4ml中に溶解し、氷冷下、冷トリフロロ酢酸4mlを加え同温度で1時間搅拌する。減圧下濃縮しイソプロピルエーテルで粉末化、洗净して乾燥する。目的物85mgを得る。

IR(ヌジョール); 1760cm<sup>-1</sup>

NMR(80MHz, δ値, ppm, DMSO-d<sub>6</sub>):

1.15 (9H, s), 3.50, 3.86 (2H, ABq, J=17.6Hz), 5.16 (1H, d, J=5Hz), 5.35 (1H, d, J=9Hz), 5.60~5.78 (2H, m), 6.75~7.10 (1H, m), 6.95 (1H, s)

NMR(80MHz, δ値, ppm, CDCl<sub>3</sub>):

1.16 (9H, s), 3.40~3.70 (7H, m), 5.10 (1H, d, J=5Hz), 5.8 (1H, d, d, J=5Hz, J=9.6Hz), 6.8 (1H, s), 6.85 (1H, s), 7.2~7.4 (26H, m)

## 実施例5

7-[2-(2-アミノチアゾール-4-イル)-2-ビバロイルオキシイミノアセトアミド]-3-メトキシカルボニルメチル-3-セフエム-4-カルボン酸ナトリウム塩:

7-[2-(2-トリチルアミノチアゾール-4-イル)-2-ビバロイルオキシイミノアセトアミド]-3-メトキシカルボニルメチル-3-セフエム-4-カルボン酸ジフェニルメチルエステル200mgをアニソール0.2mlに溶解し、これに氷冷下トリフロロ酢酸2mlを加え、同温度で30分間搅拌する。次いで減圧下濃縮し、イソプロピルエーテルで粉末化し乾燥したのち、これを水2ml-酢酸2ml中に溶解し、氷冷下2%炭酸水素ナトリウム水でpH=7.0を調整する。水層を酢酸

## 実施例4

7-[2-(2-トリチルアミノチアゾール-4-イル)-2-ビバロイルオキシイミノアセトアミド]-3-メトキシカルボニルメチル-3-セフエム-4-カルボン酸ジフェニルメチルエステル(シン異性体):

2-(2-トリチルアミノチアゾール-4-イル)-2-ビバロイルオキシイミノ酢酸256mg、7-アミノ-3-メトキシカルボニルメチル-3-セフエム-4-カルボン酸ジフェニルメチルエステル181mg、及び1-ヒドロキシベンズトリアゾール67mgを塩化メチレン20mlに溶解し氷冷する。ジシクロヘキシルカルボジイミド103mgを含む塩化メチレン1mlを加え5℃で終夜搅拌する。減圧下濃縮し、酢酸エチル30mlに溶解し不溶物を除去する。冷5%塩酸水、饱和食塩水で順次洗净し乾燥する。減圧下濃縮乾固し残渣を和光グルC-200 15gで精製する(系:トルエン-酢酸エチル)。目的物100mgを得た。

IR(ヌジョール); 3300, 1780cm<sup>-1</sup>

エチルで洗净後、ダイヤイオンHP-20 15mlを展開し精製する。目的フラクションを集め凍結乾燥し、目的物63mgを得た。

IR(ヌジョール); 1770cm<sup>-1</sup>

NMR(80MHz, δ値, D<sub>2</sub>O):

1.15 (9H, s), 3.40~3.7 (7H, m), 5.0 (1H, d, J=4.8Hz), 5.8 (1H, d, J=4.8Hz), 6.8 (1H, s)

## 実施例6

7-[2-(2-アミノチアゾール-4-イル)-2-ビバロイルオキシイミノアセトアミド]-3-(2-メトキシカルボニルビニル-3-セフエム-4-カルボン酸トリフロロ酢酸塩(シン異性体):

IR(ヌジョール); 1770cm<sup>-1</sup>

NMR(80MHz, δ値, ppm, DMSO-d<sub>6</sub>):

1.20 (9H, s), 3.4 (2H, d), 3.6 (3H, s), 5.0 (1H, d, J=4.2Hz), 5.7 (1H, d, J=1.2Hz), 5.80 (1H, d, d, J=4.2Hz, 9.6Hz), 6.7 (1H, s), 6.8 (1H, d, J=1.2Hz)

## 実施例 7

7 - [ 2 - ( 2 - ト リ チ ル ア ミ ノ チ ア ゾ ル - 4 - イ ル ) - 2 - ア セ チ ル オ キ シ イ ミ ノ ア セ ツ ア ミ ド ] - 3 - メ チ ル チ オ - 3 - セ フ エ ム - 4 - カ ル ボ ナ 酸 ジ フ エ ニ ル メ チ ル エ ス テ ル ( シ ヌ 异 性 体 ) :  
 2 - ( 2 - ト リ チ ル ア ミ ノ チ ア ゾ ル - 4 - イ ル ) - 2 - ア セ チ ル オ キ シ イ ミ ノ 酢 酸 ( シ ヌ 异 性 体 ) 1 2 0 mg 及び 7 - ア ミ ノ - 3 - メ チ ル チ オ - 3 - セ フ エ ム - 4 - カ ル ボ ナ 酸 ジ フ エ ニ ル メ チ ル エ ス テ ル 1 0 1 mg を 乾 燥 塩 化 メ チ レン 1 0 ml N C 溶 解 し、これに 1 - ヒ ド ロ キ シ ベンズ テ リ ア ゾ ル - 3 3 mg を 加 え る。冰 冷 下、ジ シ ク ロ ヘ キ シ ル カ ル ボ ジ イ ミ ド 5 0 mg を 含 む 塩 化 メ チ レン 1 ml を 加 え 5 °C で 終 夜 搅 拚 す る。不 溶 物 を 沔 取 し 2.5 % H C l 水、水 で 順 次 洗 净 後 漫 瓶 乾 固 す る。シリカゲルク ロ マ ト で 精 製 す る。( 和 光 グ ル C - 2 0 0 8 g、系 ; ト ル エ ン - 酢 酸 エ チ ル )。目的 物 1 6 0 mg を 得 る。

IR( ヌ ジ ョ ー ル ) : 1 7 7 0, 1 7 4 0 ~ 1 7 1 0 cm<sup>-1</sup>NMR( 8 0 MHz, δ 値, PPM, CDCl<sub>3</sub>, ) :

6.8 5 ( 1H, s ), 6.9 2 ( 1H, s ), 7.1 0 ~ 7.4 2 ( 2 7 H, m )

## 実施例 9

7 - [ 2 - ( 2 - ト リ チ ル ア ミ ノ チ ア ゾ ル - 4 - イ ル ) - 2 - イ ソ プ チ リ ル オ キ シ イ ミ ノ ア セ ト ア ミ ド ] - 3 - メ チ ル チ オ - 3 - セ フ エ ム - 4 - カ ル ボ ナ 酸 ジ フ エ ニ ル メ チ ル エ ス テ ル ( シ ヌ 异 性 体 ) :

NMR( 8 0 MHz, δ 値, PPM, CDCl<sub>3</sub>, ) :

1.2 0 ( 6H, d, J = 8 Hz ), 2.2 4 ( 3H, s ), 2.7 0 ( 1H, m ), 3.5 0 ( 2H, b.s ), 5.0 6 ( 1H, d, J = 5 Hz ), 5.7 5 ( 1H, d, d, J = 5 Hz, 1 0 Hz ), 6.8 6 ( 1H, s ), 6.9 0 ( 1H, s ), 7.0 5 ~ 7.3 5 ( 2 7 H, m )

## 実施例 1 0

7 - [ 2 - ( 2 - ト リ チ ル ア ミ ノ チ ア ゾ ル - 4 - イ ル ) - 2 - ピ バ ロ イ ル オ キ シ イ ミ ノ ア セ ト ア ミ ド ] - 3 - メ チ ル チ オ - 3 - セ フ エ ム - 4 - カ ル ボ ナ 酸 ジ フ エ ニ ル メ チ ル エ ス テ ル ( シ ヌ 异 性 体 ) :

2.2 0 ( 3H, s ), 2.2 6 ( 3H, s ), 3.5 4 ( 2H, b.s ), 5.0 5 ( 1H, d, J = 5.0 Hz ), 5.7 5 ( 1H, d, d, J = 5.0 Hz, 9.0 Hz ), 7.8 6 ( 1H, s ), 7.9 0 ( 1H, s ), 7.0 0 ~ 7.4 5 ( 2 7 H, m )

実施例 7 と 同 様 に 2 - ( 2 - ト リ チ ル ア ミ ノ チ ア ゾ ル - 4 - イ ル ) - 2 - ア ル キ ル ア シ ル オ キ シ イ ミ ノ 酢 酸 及 び 対 応 す る 7 - ア ミ ノ - 3 - セ フ エ ム - 誘導 体 を 用 いて 実 施 例 8 ~ 1 1 の 化 合 物 を 得 る。

## 実施例 8

7 - [ 2 - ( 2 - ト リ チ ル ア ミ ノ チ ア ゾ ル - 4 - イ ル ) - 2 - プ ロ ピ オ ノ イ ル オ キ シ イ ミ ノ ア セ ト ア ミ ド ] - 3 - メ チ ル チ オ - 3 - セ フ エ ム - 4 - カ ル ボ ナ 酸 ジ フ エ ニ ル メ チ ル エ ス テ ル ( シ ヌ 异 性 体 ) :

IR( ヌ ジ ョ ー ル ) : 1 7 7 0, 1 7 4 0 ~ 1 7 1 0 cm<sup>-1</sup>NMR( 8 0 MHz, δ 値, PPM, CDCl<sub>3</sub>, ) :

1.2 5 ( 3H, t, J = 8 Hz ), 2.2 6 ( 3H, s ), 2.4 8 ( 2H, q, J = 8 Hz ), 3.5 5 ( 2H, b.s ), 5.0 6 ( 1H, d, J = 5 Hz ), 5.7 5 ( 1H, d, d, J = 5 Hz, 9 Hz ),

NMR( 8 0 MHz, δ 値, PPM, CDCl<sub>3</sub>, ) :

1.2 7 ( 9H, s ), 2.2 6 ( 3H, s ), 3.3 5, 3.6 5 ( 2H, ABq, J = 1 6 Hz ), 5.0 3 ( 1H, d, J = 5 Hz ), 5.7 8 ( 1H, d, d, J = 5 Hz, 9 Hz ), 6.9 0 ( 1H, s ), 6.9 5 ( 1H, s ), 7.1 5 ~ 7.4 0 ( 2 7 H, m )

## 実施例 1 1

7 - [ 2 - ( 2 - ト リ チ ル ア ミ ノ チ ア ゾ ル - 4 - イ ル ) - 2 - ピ バ ロ イ ル オ キ シ イ ミ ノ ア セ ト ア ミ ド ] - 3 - エ チ ル チ オ - 3 - セ フ エ ム - 4 - カ ル ボ ナ 酸 ジ フ エ ニ ル メ チ ル エ ス テ ル ( シ ヌ 异 性 体 ) :

IR( ヌ ジ ョ ー ル ) : 3 3 0 0, 1 7 8 0, 1 7 4 0 ~ 1 7 2 0 cm<sup>-1</sup>NMR( 8 0 MHz, δ 値, PPM, CDCl<sub>3</sub>, ) :

1.2 0 ( 3H, t, J = 8 Hz ), 1.2 5 ( 9H, s ), 2.7 0 ( 2H, q, J = 8 Hz ), 3.4 5 ( 2H, b.s ), 5.0 5 ( 1H, d, J = 4.8 Hz ), 5.7 0 ( 1H, d, d, J = 4.8 Hz, J = 9 Hz ), 6.8 5 ( 1H, s ), 6.9 0 ( 1H, s ), 7.1 5 ~ 7.3 2 ( 2 6 H, b.s )

## 実施例 1 2

7-[2-(2-アミノチアゾール-4-イル)-2-アセチルオキシイミノアセトアミド]-3-メチルチオ-3-セフエム-4-カルボン酸トリフロロ酢酸塩(シン異性体)：

7-[2-(2-トリチルアミノチアゾール-4-イル)-2-アセチルオキシイミノアセトアミド]-3-メチルチオ-3-セフエム-4-カルボン酸ジフェニルメチルエステル150mgをアニソール0.2ml中に氷冷下に加え溶解する。同温度で更にトリフロロ酢酸2mlを加え、氷冷下1時間攪拌する。

トリフロロ酢酸を減圧下20°Cで濃縮し、残渣にイソプロピルエーテルを加え粉末化する。イソプロピルエーテル、エーテルで十分洗浄後、遠心分離機で分離する。減圧下乾燥し目的物55mgを得る。

IR(ヌジョール)；1770cm<sup>-1</sup>

NMR(80MHz, δ値, ppm, DMSO-d<sub>6</sub>)；

2.16(3H, s), 2.32(3H, s), 3.75(2H, s), 5.12(1H, d, J=4.8Hz), 5.68(1H, d, d, J=

4.8Hz, J=7.5Hz), 7.10(1H, s), 9.78(1H, d, J=7.5Hz)

実施例12と同様に対応する保護された3-セフエムセフアロスボリン化合物の保護基をトリフロロ酢酸により除去し、次の実施例13～16の化合物を得た。

#### 実施例13

7-[2-(2-アミノチアゾール-4-イル)-2-ブロビオノイルオキシイミノアセトアミド]-3-メチルチオ-3-セフエム-4-カルボン酸トリフロロ酢酸塩(シン異性体)：

IR(ヌジョール)；1760cm<sup>-1</sup>

NMR(80MHz, δ値, ppm, DMSO-d<sub>6</sub>)；

1.25(3H, t, J=8Hz), 2.26(3H, s), 2.50(2H, q, J=8Hz), 5.05(1H, d, J=5.0Hz), 5.70(1H, d, d, J=5.0Hz, J=8Hz), 7.05(1H, s), 9.80(1H, d, J=8Hz)

#### 実施例14

7-[2-(2-アミノチアゾール-4-イル)-2-イソブチリルオキシイミノアセトアミド]：

-3-メチルチオ-3-セフエム-4-カルボン酸トリフロロ酢酸塩(シン異性体)：

IR(ヌジョール)；1760cm<sup>-1</sup>

NMR(80MHz, δ値, ppm, DMSO-d<sub>6</sub>)；

1.15(6H, d, J=7.5Hz), 2.3(3H, s), 2.65(1H, m), 3.70(2H, b.s), 5.15(1H, d, J=5Hz), 5.70(1H, d, d, J=5Hz, J=8.2Hz), 7.05(1H, s), 9.85(1H, d, J=8.2Hz)

#### 実施例15

7-[2-(2-アミノチアゾール-4-イル)-2-ビバロイルオキシイミノアセトアミド]-3-メチルチオ-3-セフエム-4-カルボン酸トリフロロ酢酸塩(シン異性体)：

IR(ヌジョール)；3300, 1770cm<sup>-1</sup>

NMR(80MHz, δ値, ppm, DMSO-d<sub>6</sub>)；

1.20(9H, s), 2.30(3H, s), 3.75(2H, b.s), 5.15(1H, d, J=5Hz), 5.70(1H, d, d, J=5Hz, J=9Hz), 7.05(1H, s), 9.85(1H, d, J=9Hz)

#### 実施例16

7-[2-(2-アミノチアゾール-4-イル)-2-ビバロイルオキシイミノアセトアミド]-3-エチルチオ-3-セフエム-4-カルボン酸トリフロロ酢酸塩(シン異性体)：

IR(ヌジョール)；1760cm<sup>-1</sup>

NMR(80MHz, δ値, ppm, DMSO-d<sub>6</sub>)；

1.20(3H, t, J=8Hz), 1.25(9H, s), 2.70(2H, q, J=8Hz), 3.70(2H, b.s), 5.15(1H, d, J=5Hz), 5.72(1H, d, d, J=5Hz, J=8Hz), 7.1(1H, s), 9.80(1H, d, J=8Hz)

#### 実施例17

7-[2-(2-トリチルアミノチアゾール-4-イル)-2-アセチルオキシイミノアセトアミド]-3-メチルチオ-3-セフエム-4-カルボン酸ビバロイルオキシメチルエステル(シン異性体)：

2-(2-トリチルアミノチアゾール-4-イル)-2-アセチルオキシイミノ酢酸(シン異性体)120mg及び7-アミノ-3-メチルチオ-3-セフエム-4-カルボン酸ビバロイルオキシ

実施例17と同様にして対応する3-セフエム化合物より標記化合物を得た。

NMR(80 MHz, δ値, PPM, CDCl<sub>3</sub>) ;

1.25(9H, s), 1.30(9H, s), 2.35(3H, s),  
3.55(2H, b.d), 5.10(1H, d, J=5Hz),  
5.60~5.95(3H, m), 6.85(1H, d, J=8Hz),  
6.95(1H, s), 7.20~7.35(16H, m)

## 実施例19

7-[2-(2-アミノチアゾール-4-イル)-

-2-アセチルオキシイミノアセトアミド]-3-メチルチオ-3-セフエム-4-カルボン酸ビバロイルオキシメチルエステル(シン異性体) :

7-[2-(2-トリチルアミノチアゾール-4-イル)-2-ビバロイルオキシイミノアセトアミド]-3-メチルチオ-3-セフエム-4-カルボン酸ビバロイルオキシメチルエステル(シン異性体) 100mgをアニソール0.1ml中に加え氷冷する。次いでトリフロロ酢酸1ml加え、同温度で1時間搅拌し減圧下濃縮する。イソプロピルエーテルを加え粉末化し十分にイソプロピルエーテ

メチルエステル90mgを乾燥塩化メチレン10mlに溶解し、これに1-ヒドロキシベンズトリアゾール33mgを加える。次いで氷冷下ジシクロヘキシカルボジイミド50mgを含む塩化メチレン1mlを加える。5℃で終夜搅拌し不溶物を沪取し2.5g HCl、水で順次洗净する。乾燥後、減圧下濃縮乾固したのちシリカゲルクロマトタに付し精製する。目的物130mgを得る。

IR(ヌジョール) ; 3300, 1770, 1740 ~  
1710 cm<sup>-1</sup>

NMR(80 MHz, δ値, PPM, CDCl<sub>3</sub>) ;  
1.20(9H, s), 2.15(3H, s), 2.3(3H, s),  
3.55(2H, b.s), 5.05(1H, d, J=4.8Hz),  
5.15~5.35(3H, m), 6.85(1H, s), 6.95(1H, d, J=8Hz), 7.15~7.35(16H, m)

## 実施例18

7-[2-(2-トリチルアミノチアゾール-4-イル)-2-ビバロイルオキシイミノアセトアミド]-3-メチルチオ-3-セフエム-4-カルボン酸ビバロイルオキシメチルエステル：

ル、エーテルで順次洗净する。粉末を酢酸エチル10mlに溶解し、氷冷下5%重炭酸ナトリウム水溶液でpH=7.0に調整する。有機層を水洗後、硫酸マグネシウムで乾燥する。濃縮乾固し目的物38mgを得る。

IR(ヌジョール) ; 1760 cm<sup>-1</sup>

NMR(80 MHz, δ値, PPM, CDCl<sub>3</sub>) ;  
1.25(9H, s), 2.20(3H, s), 2.35(3H, s),  
3.60(2H, b.s), 5.10(1H, d, J=5Hz),  
5.70~5.95(3H, m), 6.90(1H, s), 8.25(1H, d, J=8Hz)

## 実施例20

7-[2-(2-アミノチアゾール-4-イル)-2-ビバロイルオキシイミノアセトアミド]-3-メチルチオ-3-セフエム-4-カルボン酸ビバロイルオキシメチルエステル(シン異性体) :

実施例19と同様にして標記化合物を得た。

NMR(80 MHz, δ値, PPM, CDCl<sub>3</sub>) ;  
1.25(9H, s), 1.30(9H, s), 2.35(3H, s),  
3.65(2H, b.s), 5.10(1H, d, J=5Hz),

5.70~5.95(3H, m), 6.95(1H, s), 7.60(1H, d, J=8Hz)

以上

出願人 明治製菓株式会社

代理人 弁理士 有賀三郎



弁理士 高野登志雄



弁理士 小野信夫



手続補正書(自発)

昭和58年10月18日

特許庁長官 若杉和夫 殿

## 1. 事件の表示

昭和58年 特許第565号

## 2. 発明の名称

新規セフエム化合物

## 3. 補正をする者

事件との関係 出願人

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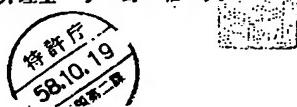
氏名 (7756)弁理士高野登志雄

住所 同上

氏名 (8632)弁理士小野信夫

## 5. 補正命令の日付

自発



## 6. 補正の対象

明細書の「発明の詳細な説明」の欄

## 7. 補正の内容

## (1) 明細書中、第4頁第10行、

「で表わされる化合物を脱保護基として---

---」とあるを、

「で表わされる化合物のR<sub>1</sub><sup>a</sup>の脱保護反応に付  
して-----」と訂正する。

## (2) 同、第7頁第9行、

「オキシムイミノ基」とあるを、

「オキシイミノ基」と訂正する。

## (3) 同、同第12行、

「還元的に」とあるを、削除する。